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14. ABSTRACT

Purpose: The purpose of this study is to determine if rapid acquisition diffusion tensor imaging (DTI) in conjunction with conventional magnetic resonance imaging (MRI) can be used as a reliable surrogate for assessing extent of neurologic injury and potential for recovery after spinal cord injury (SCI).
Methods: 23 SCI patients and 40 control subjects were employed in this study. An MRI/DTI was obtained at initial admission, prior to surgical intervention. Full INSCSCI neurologic evaluation was performed at five time points up to six months after injury. MRI and DTI indices were compared to interval neurologic status and recovery trajectories.
Results: Spinal cord hemorrhage and edema on anatomic MRI, and FA, ADC, RD and AD indices derived from DTI data correlate significantly to temporal neurologic parameters that assess extent of neurologic deficit. MRI and DTI indices have a relationship to neurologic recovery parameters.
Conclusions: MRI and DTI are valid and objective tools for gauging extent of neurologic injury after SCI and could play a role in helping to forecast potential for recovery in lieu of or as a complementary role to neurologic evaluation.

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Introduction

Use of MRI/DTI may improve accuracy in stratifying SCI patients that are being selected for clinical trials to test novel therapies. Trials which utilize MRI/DTI at the point of entry have the potential to demonstrate therapeutic efficacy with fewer patients. The objective of our proposal is to prove that the MRI features of SCI and DTI when used in conjunction with the initial neurologic assessment will provide a better method to classify patients during their initial hospitalization and will better discriminate patients that have capacity for spontaneous functional recovery from those with no inherent capacity for recovery. The results derived from this project have the capacity to radically alter the methods by which we categorize SCI at the point of entry into the healthcare system by more accurately characterizing the extent of their injuries and providing the opportunity to administer appropriate therapies in the critical few hours after injury. This has direct benefit to the individual patient and their families in gauging expectations for recovery and in selecting patients for novel therapies. The goal of this study is to combine the information obtained from the physical examination of the SCI patient at the time of injury with the anatomic and physiologic information provided through MRI and DTI to better predict which patients might realize the most benefit from a new medication. If the added value of MRI and DTI improves the pre-selection process of patients for a new medication, this could also provide a secondary benefit in helping to expedite the drug approval process by decreasing the number of patients required to prove that the drug actually benefits patients.

Keywords

Spinal cord injury, magnetic resonance imaging, MRI, diffusion tensor imaging, DTI, neurologic recovery.

Overall Project Summary

Background

Spinal cord injury (SCI) is a devastating, life-altering event. Approximately 12,000 new injuries occur annually in the United States (1), and currently there are approximately 227,080 to 300,938 individuals living in the U.S. with the sequelae of SCI including permanent paralysis. Not surprisingly, the costs to society of SCI are staggering and in 1998 were estimated at $9.7 billion per year (2). The lifetime direct costs of a high tetraplegic injured at age 25 can exceed $3 million (1). Males are disproportionately affected with a 4:1 male-to-female ratio, and the majority of injuries occur between the ages of 16 and 30. Mirroring the increasing age of the U.S. general population, the average age at injury has increased from 28.7 years of age in the mid-1970s to 39.5 years since 2005.

There are currently no "cures" for SCI and the only accepted pharmacologic treatment regimen for traumatic SCI is high dose methylprednisolone (MP) which has been reported to show efficacy in Phase II randomized trials (3). Subsequently, MP administration for acute SCI has become widespread in the United States. Recently the efficacy of this treatment has been questioned and currently is the subject of ongoing debate (4, 5). Much of the debate has centered on whether the magnitude of reported improvement with MP is clinically important. The controversy regarding the utilization of MP highlights the critical need for new treatment strategies. To date, the treatment of acute SCI has been characterized, unfortunately, by the paucity of clinical trials. Although the efficacy and safety of MP remains controversial, there is general agreement that any pharmacologic measure should be employed in the first few *hours* after injury. Patient selection for a specific therapy can be problematic in the acute period because the classification system used to grade neurologic impairment is completely dependent upon the accuracy of the neurologic examination. The neurologic examination is accurate and reproducible in ideal conditions. However, the results can vary substantially based upon the level of cooperation, communication and consciousness of the patient, associated patient comorbidities and the skills of the examiner. Moreover, the full extent of a patient's neurologic injury may not become apparent for days after injury. By then, late implementation of a drug based upon a delayed neurologic assessment is less likely to demonstrate a therapeutic response. The goal of this proposal is to determine if the metrics derived from conventional magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) in conjunction with the neurological exam can serve as a reliable objective biomarker for determination of the extent of neurologic injury and early identification of patients who would benefit from treatment.

In general, spontaneous neurologic recovery from SCI is inversely related to the severity of the initial neurologic injury. However, there is reported variability in recovery within similar American Spinal Injury Association Impairment Scale (AIS) grades. The majority of neurological recovery in SCI patients occurs during the first 6-9 months (6-8). Afterwards, the rate of improvement rapidly drops off with a plateau being reached 12-18 months post-injury with little additional improvement after that time. Early improvement in neurological status is associated with greater recovery than slow improvement (9). Late recovery following complete SCI, defined as motor recovery greater than one year after injury, is rare but can occur. Recovery of motor function distal to the zone of injury in patients with complete SCI is relatively rare, and when it does occur it tends to be minimal and nonfunctional. The national SCI database indicates that about 15% of all AIS grade A patients admitted within one week of injury convert to incomplete status by one year. However, only 2.3% of initially complete patients regain significant motor function below the injury level, that is, to AIS grade D (10). Other studies have reported complete to incomplete conversion rates ranging from 4 to 34% (6, 7, 11-13). Recovery in motor complete, sensory incomplete injuries (AIS grade B) is mixed, with about 50% attaining ambulatory status (14, 15). By definition, individuals with an AIS grade B injury have some initial preservation of distal sensation, including the S4-5 dermatomes, but no accompanying motor function. Continuity of sensory preservation between the neurological level of injury (NLI) and the S4-5 dermatome is not required. It is known that this type of sensory sparing influences prognosis – those with sacral or lower extremity pin prick sensation – have a better chance of walking than those with only light touch sensation (15-19).

While recovery in motor complete injuries is generally poor, recovery from incomplete injuries (AIS grades C and D) is generally good, although this is influenced by the degree of motor deficit and the age of the patient. For AIS grade C patients younger than 50 years of age at the time of injury, the chance of walking exceeds 90%, while those over age 50 have only a 42% chance of walking (20). Up to 95% of individuals with AIS grade D injuries will recover the ability to ambulate (14). Part of the reason for this wide recovery range is the difficulty associated with performing an accurate neurological assessment during the early phase of injury and the inherent inaccuracy in classifying the initial deficit correctly. Factors that can impact reliability include those affecting cognition (traumatic brain injury, drug effects, and psychological disorders) as well as communication (ventilator dependency, language barrier) (21).

In contrast to recovery below the zone of injury, most people with complete tetraplegia have some local recovery immediately cephalad to the zone of injury (i.e. the zone of partial preservation or ZPP). The majority of individuals with complete tetraplegia gain a motor level, although there are differences dependent on the initial level. If the initial motor level is C4, 70% will gain C5 motor function; the corresponding rates for C5 to C6 and C6 to C7 are 75% and 85%, respectively (8). Recovery more than two levels below the most caudal level with motor function is rare, being seen in only 1% of cases (7). Early improvement in neurological status is associated with greater recovery than slow improvement. Late recovery following complete SCI, defined as motor recovery greater than one year after injury, is rare but can occur. Because there are significant reported variations in the degree of spontaneous recovery within similar impairment groups, the creation of novel objective criteria that can discriminate patients with inherent capacity for spontaneous recovery from those with minimal capacity to recover would be extremely valuable in selecting patients for a therapeutic option and for gauging efficacy of the therapy.

One factor that accounts for this wide range in recovery is attributed the difficulty associated with performing an accurate neurological assessment during the early phase of injury. Influences that can impact reliability of this clinical examination include those affecting cognition (traumatic brain injury, drug effects, and psychological disorders) as well as communication (ventilator dependency, language barrier (21). There is a potential therefore to initially misclassify patients at the time of presentation which can lead to under or overestimation of degree of recovery on follow-up examination. It is this potential for misclassification that contributes to ambiguity in our understanding of the relationship of the initial injury to spontaneous recovery. Moreover, as new novel therapies for SCI become routinely available, it is imperative that we improve our precision in classifying patients as close as possible to the time of injury in order to maximize benefits of these therapies. Other objective methodologies are needed for identifying appropriate patient populations for treatment delivery; optimal therapy may need to be delivered in the first few hours or days, yet neurologic examination may require a week's delay before providing an accurate prognosis (21). Therefore there is a motivation to diminish the inherent subjectivity of the initial neurologic assessment as much as possible.

The variability in recovery for patients with incomplete SCI has hindered the study of promising treatments in the acute injury period for such patients. As a panel sponsored by the International Campaign for Cures of Spinal Cord Injury Paralysis (ICCP) reported " [t]rials involving motor incomplete SCI patients, or trials where an accurate assessment of AIS grade cannot be made before the start of the trial, will require large subject numbers and/or better objective assessment methods." (22). For example, to detect a 10-point difference in motor score recovery between groups of patients with cervical complete SCI (AIS grade A) would require 60 subjects in each arm of the study. This number jumps to 277 subjects per group if the study involves AIS grade B patients (22). The substantial variability in recovery within similar injury classification suggests that the arbitrary delineation among injury classifications (AIS: A – E) may not be representative of all of the potential functional categories. Potentially functional subclasses may exist that need to be defined through means other than the neurologic examination, such as MRI. With this additional information, the ability to perform rigorous patient selection prior to initiation of

therapy would be greatly enhanced and measuring efficacy of these therapies would be much more feasible.

Currently, MRI provides the only means to directly inspect the damaged spinal cord, therefore it has the potential to complement the assessment provided by the subjective neurologic examination in gauging the degree of injury in SCI. Moreover, MRI evaluation is not operator dependent and the assessment of the MRI features is reproducible among observers. MRI provides excellent definition of intramedullary hemorrhage and edema in animal models. The combination of MRI lesion length, cord caliber, and degree of preservation of white matter in MRI cross-section has a significant relationship to functional status in animals and the pathologic findings at autopsy. The MRI appearance of experimentally induced SCI has been used to explain the variability in functional deficit among animals subjected to identical injuries. A significant shortcoming of MRI is its limited capability in demonstrating preserved white matter tracts at the level of injury; this observation becomes significant in estimating preserved functional capacity. With the advent of diffusion techniques and tractography algorithms based upon diffusion parameters, MRI now has the capacity to assess the integrity of spinal white matter. The depiction of parenchymal SCI on MRI not only correlates well with the degree of neurologic deficit, but it also bears significant implications with regard to prognosis and potential for neurologic recovery (23-29).

Many clinical investigations have reported that the MRI patterns of SCI correlate with the neurologic deficit at presentation. Kulkarni et al. initially proposed three MRI injury patterns for SCI and correlated these with the five-part AIS and total motor scores. Intramedullary hemorrhage (Type I pattern of injury) equated with a severe neurologic deficit and a poor prognosis. Cord edema alone (Type II pattern of injury) was found in patients with mild to moderate initial neurologic deficits who subsequently showed neurologic improvement (28).

Schaefer et al. refined the MRI patterns of SCI by including the size of the injured segment (26). Cord edema that extended for more than the span of one vertebral segment was associated with a more severe initial deficit than smaller areas of edema. Cord hemorrhage was associated with the most severe neurologic abnormalities (26). Flanders et al. (24) demonstrated that spinal cord hemorrhage in the cervical region was a strong predictive finding for a complete neurologic injury. The location of the hemorrhage corresponded anatomically to the level of neurologic injury. Although the location of spinal cord edema related imprecisely to the neurologic level, the proportion of spinal cord affected by edema was directly related to the severity of initial neurologic injury.

Schaefer et al. correlated the MRI appearance of the spinal cord on admission to the change in total motor index score (MIS) in 57 patients (27). Patients with hemorrhagic spinal cord lesions showed no statistical improvement in motor index score at follow-up. The group of patients with small areas of edema (less than one vertebral segment in length) demonstrated the largest improvement in MIS (72% recovery), whereas larger areas of edema showed intermediate recovery of MIS (42%) (27).

Flanders et al. assessed the prognostic capabilities of MRI in forecasting motor recovery in 104 cervical SCI patients (23). Individual manual muscle test scores were compiled for the upper and lower extremities both at the time of admission and twelve months after injury. A motor recovery rate for the upper and lower extremities was also determined. The injured spinal cord segment on MRI was measured using a unique method that quantified spinal cord hemorrhage and edema by length and location relative to known anatomic landmarks. Lesion length was directly proportional to neurologic impairment at the time of injury ($p < .001$). In addition, spinal cord hemorrhage was associated with the most severe injuries ($p < .001$). While improvement in motor function after one year was observed in all patients, subjects with spinal cord hemorrhage on MRI had lower initial motor scores and had less improvement than those without hemorrhage. Non-hemorrhagic MRI lesions were associated with significantly higher motor recovery rates in the lower and upper extremities and had a higher proportion of useful muscle function. Multiple regression analysis was used to determine the contribution of MRI in predicting the outcomes parameters of motor function independent of the initial clinical evaluation. Initial motor scores, the

presence of hemorrhage and the length of edema were independent predictors of final motor score and the proportion of muscles with useful function at one year. The addition of the MRI parameters to the initial clinical information improved the statistical power of the SCI model by 16% for the upper extremities and 34% for the lower extremities. (23)

Flanders et al. also compared the MRI parameters of edema and hemorrhage to a standardized measurement of disability (functional independence measure (FIM)) (30). Four distinct motor scales from the FIM assessment were determined at the time of admission to rehabilitation and subsequently at discharge from rehabilitation. The individual motor scales included tasks related to self-care, sphincter control, mobility and locomotion. Patients without spinal cord hemorrhage on MRI had significant improvement in self-care and mobility scores compared to patients with hemorrhage. The upper limit of the lesion (edema) correlated with admission and discharge self-care, admission mobility and locomotion scores. Edema length correlated negatively with all FIM scores at admission and discharge. Moreover, at the time of admission to rehabilitation, all patients were completely dependent on equipment or caregivers to perform the FIM tasks. At the time of discharge, only patients with non-hemorrhagic MRI lesions improved to a modified dependence category (30).

Boldin et al. did a prospective analysis of 29 SCI patients by comparing an absolute measurement of the size of the injured segment on a post-operative MRI to the initial clinical examination and changes in long-term neurologic status (31). The authors also found that the presence of intramedullary hemorrhage had a higher association with a complete neurologic deficit and patients with hemorrhages that measured greater than 4 mm in cranial-caudal length showed no clinical improvement at follow-up. Both the length of edema and hemorrhage were shown to be predictive variables for complete injuries. Patients with hemorrhages measuring less than 4mm had incomplete injuries upon admission and showed clinical improvement at follow-up. While their patient cohort was small and the authors were unable to control for time to clinical follow-up or time to imaging, their data suggest that there may be an absolute threshold for lesion size that predicts neurologic recovery (31).

Boghosian et al. correlated the NLI with the anatomic location of the spinal cord lesions on the MRIs of 109 cervical spinal cord injured patients (32). The authors found a statistically significant correlation between the location of the upper margin of spinal cord edema and hemorrhage as well as the lesion epicenter. The upper boundary of hemorrhage showed a stronger correlation than either edema or lesion epicenter. The lesion length showed no statistical significance with NLI. Lesion epicenter and edema length were the best predictors of NLI. The implication of this work is that some MRI measures may be used as an objective measure of the NLI when determination by clinical examination is either inaccurate or unavailable (32).

While MRI is the best imaging modality for the evaluation of spinal cord parenchyma, conventional MR techniques do not appear to differentiate edema from axonal injury, are therefore limited to providing anatomic information about the spinal cord parenchyma. The water content or hemorrhagic content does not necessarily reflect the status of the white matter tracts and consequently the functional status of the spinal cord is not well assessed.

As with white matter tracts in the brain, anisotropy in the spinal cord appears to be due to diffusion barriers encountered as water moves in the direction perpendicular to the fibers. These barriers are believed to be cellular membranes and myelin sheaths, which result in a low transverse apparent diffusion coefficient (tADC). As water diffuses longitudinally in the spinal cord, these diffusion barriers are not encountered, and the longitudinal apparent diffusion coefficient (lADC) is therefore large in comparison to tADC. Using either diffusion-weighted imaging (DWI) or DTI techniques, the preferred direction of anisotropic water diffusion in spinal cord white matter tracts has been shown in numerous ex vivo (33-39) and in vivo (40-47) experimental studies, as well as in vivo human studies (48-56), to be parallel, or longitudinal, to the long axis of the axons.

A critical goal of spinal cord imaging research is a non-invasive quantifiable predictor of axon loss. Schwartz et al. has shown that the natural variation of differing axon morphometric parameters (including axon density, axon spacing, axon diameter) between normal spinal cord tracts significantly correlates with different directional water diffusion values (57). Ford et al. showed that alterations in ADC values were more sensitive than conventional MR techniques in detecting experimental spinal cord injury (58). Following injury, tADC values increased and lADC values decreased in both normal and abnormal appearing white matter. These changes resulted in decreased anisotropy. These results imply that there are consequences of spinal cord injury that dramatically alter axon structure without changing water content or T2, and therefore would not be detected by conventional MR imaging. Nevo et al. has shown that measurement of ADC values and anisotropy can be used to quantify spinal cord injury and neuroprotection (37). Changes in apparent diffusion coefficients in spinal cord white matter have been correlated with behavioral recovery following cervical lateral funiculus lesion and transplantation of fibroblasts genetically modified to express brain derived neurotrophic factor (BDNF) (34).

The earliest case report which utilized DWI in acute human SCI it was noted that diffusion values decreased acutely at the site of injury, potentially due to cellular and axonal swelling (59). In another case report of a patient with syringomyelia, DTI was able to identify spared white matter around the periphery of the syrinx, underscoring the potential for visualizing spared white matter following trauma (60). In patients with spondylosis and spinal cord compression, it has been seen that diffusion MRI improves sensitivity to cervical myelopathy, however there have been conflicting reports of both increased and decreased ADC values, and it may be that the age and clinical severity of a lesion may be important in relating the imaging finding to pathophysiology (61, 62). DTI may also be able to determine the degree and directionality of glial scarring in the gray following injury, which may go undetected with conventional MRI (63,64). As some current therapies are focused on decreasing the degree of glial scarring following injury, DTI may provide an important non-invasive outcome measure.

Although the majority of published works on the application of DTI in SCI utilize animal models, there are limited published series that illustrate the utility of DTI in *human* spinal cord injury (64-73). Ellingson et al. reported significant decreases in FA and MD in a group of chronic spinal cord injured patients compared to normal controls. MD was measurably lower throughout the spinal cord in the injured group and FA reduction was indirectly related to clinical severity (68,69). In a small clinical series, Shanmuganathan et al. demonstrated the feasibility of clinical DTI in *acute* SCI by reporting a consistent change of DTI parameters in twenty SCI patients compared to normal controls using a standard clinical MRI unit (71). Whole cord ADC values were significantly lower in patients and both the ADC values and fractional anisotropy (FA) values were decreased at the site of injury compared with controls. Interestingly, the authors reported a decrease in regional ADC values remote from the site of injury suggesting that the DTI parameters can vary in normal appearing spinal cord on conventional MRI. This supports the concept that DTI may have greater value in mapping the full extent of injury in conjunction with features from conventional MRI. In a subsequent study, Cheran et al. found statistically significant differences in mean diffusivity (MD), fractional anisotropy (FA), radial (RD) and longitudinal diffusivity (AD) for hemorrhagic and non-hemorrhagic SCI patients compared to controls (72). For non-hemorrhagic SCI, the investigators found strong correlations between admission motor scores (total MIS) and average MD, FA, RD and AD at the injury site. This same relationship did not hold for hemorrhagic SCI. In a small cohort of human cervical SCI patients, Chang found that DTI indices correlated better than conventional anatomic MRI (73).

Preliminary Studies

A preliminary study to assess the feasibility of obtaining clinically useful DTI data in a series of spinal trauma patients with and without clinical evidence of spinal cord injury. The goal was to determine if alterations in MR diffusion characteristics can serve as an objective surrogate for neurologic deficit in acute human SCI. By mapping DTI metrics relative to the injury and normal appearing spinal cord, it was postulated that alterations in DTI values may be measurable throughout the length of the spinal cord offering supplemental information regarding impairment (Figure 1).

Patients were scanned according to site clinical protocol, with either a multi-element spine coil or a neurovascular array coil at 1.5 or 3T (Achieva, Philips Healthcare, Netherlands). Structural scans including T1- and proton density-weighted turbo spin-echo and fat-suppressed T2-weighted scans were performed in the sagittal plane. Axial scans included a fat-suppressed balanced scan, a T2-weighted scan and the DTI acquisition. A diffusion weighted imaging acquisition of the entire cervical spinal cord was supplemented to the clinical MRI protocol used for spinal trauma admissions to our facility. The DTI acquisition required approximately 3:40 at 1.5T using six directions (1) and four signal averages, using 128x128 resolution (0.95 mm voxels) TR/TE: 2500/75 msec; b=500; FOV 22 cm; slice thickness 4 mm; 128x128 matrix; 0.95 mm3 voxels. The acquisition resulted in approximately 24-36 continuous axial images of the entire cervical spinal cord. The mean FA and apparent diffusion coefficient (ADC) from 2D regions of interest (ROIs) encompassing the entire cross-sectional area of the spinal cord were used for quantitative comparison at each of the slice locations. Slices were mapped to anatomical location and referenced against location of spinal cord edema (Figure 1). Values were compared to twelve normal control datasets and stratified by neurologic deficit that included the ASIA impairment scale (AIS), the neurological level of injury (NLI) and demographics. Regions-of-interest were obtained of the entire cross section of spinal cord from each axial section. The location of the DTI section ROI was anatomically mapped to the nearest location relative to the adjacent vertebral body on reference T2 weighted images (Figure 1). DTI slice locations were also mapped to the span of injury in the visible damaged segment of spinal cord on sagittal T2 weighted images. Whole slice fractional anisotropy (FA), apparent diffusion coefficient (ADC) and radial diffusivity were calculated for each of the selected slices and mapped to the location of the injured spinal cord segment and normal appearing spinal cord. Patients were stratified by the ASIA impairment scale (AIS) and mean values for calculated for each clinical impairment subgroup.

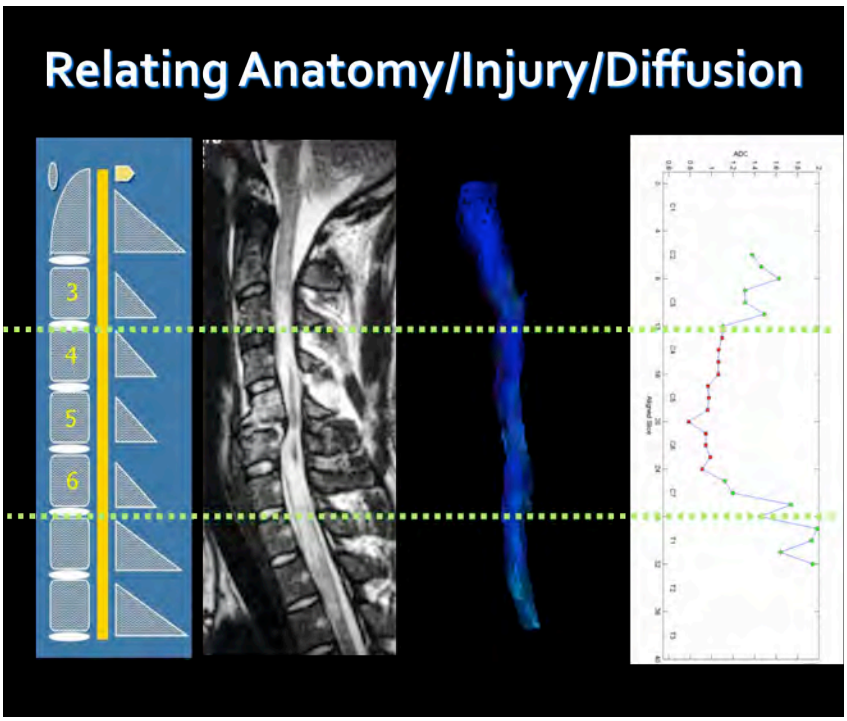

Figure 1. Mapping span of injury to anatomic location with conventional MRI and diffusion metrics.

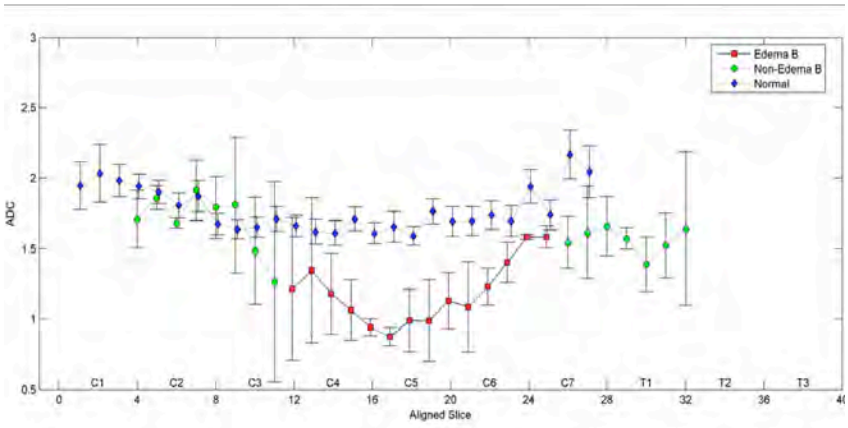

Figure 2. Plot of ADC values relative to anatomic location in the spinal cord for AIS grade B spinal cord injured subjects and normal controls.

28 patients were used for this preliminary analysis which included sixteen patients with confirmed neurologic impairment (AIS A-D) and twelve controls with no clinical or MRI findings of SCI (AIS E). The study cohort

consisted of: AIS A (6), AIS B (3), AIS C (3), AIS D (4). Fiber tracking from a single 3D-connected seed was used for initial evaluation of the data quality; the mean FA and ADC from the resulting fiber bundles were used for comparison.

Aggregate ADC values of the subgroup of patients with AIS B were mapped relative to anatomic location in the cervical spine (Figure 2). There was reduction in mean ADC values in the injured spinal cords relative to normal controls (blue points). Moreover, the change in ADC values was largest in the section of cord that displayed corresponding areas of edema on T2 weighted images (red points) and the values in normal appearing spinal cord in the injured subgroup (green points) differed from normal controls.

A DWI map for an individual patient with a C3 AIS grade A injury is shown in Figure 3. The largest deviation in FA and ADC values corresponded anatomically to anatomic epicenter of the injury on the T2 weighted image (red circle). The boundaries of the injured segment on the sagittal images (dashed yellow lines) show a progressive change in diffusion values corresponding to the proximity to the center of injury. A similar relationship between diffusivity and proximity to the location of injury has been described in animal models (34). An unexpected finding was that the FA values consistently showed an increase at the lesion epicenter whereas all animal models of acute SCI and the few human studies report a decrease in anisotropy. This observation remains unexplained.

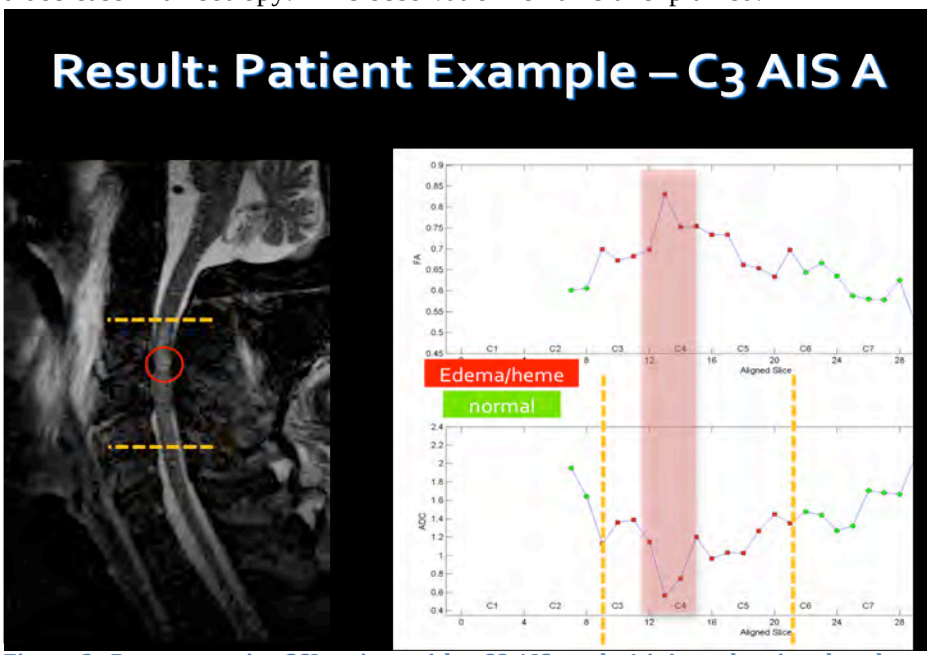

Figure 3. Representative SCI patient with a C3 AIS grade A injury showing that the largest perturbation in ADC and FA values occurs at lesion epicenter.

The FA values derived from fiber tracking (0.619 +/- 0.17) in the neurologically intact (normal controls) were commensurate with published values (69, 70). The mean diffusion values stratified by each ASIA group (A-D) and normals (N) were - FA: (A) 0.64+/-.07,(B) 0.62+/-.07, (C) 0.59+/-.07, (D) 0.64+/-.07, (N) 0.57+/-.08 and ADC: (A) 1.17+/-0.3, (B) 1.18+/-0.4, (C) 1.49+/-0.3, (D) 1.19+/-0.3, (N) 1.76+/-0.4. There was significant reduction in ADC values and elevation in FA values for the spinal cord injured patients in all four injury classifications relative to normals, ($p<.001$).

The results of this preliminary work suggest that the rapid acquisition DTI technique utilized is clinically feasible even in the acute trauma setting. The data derived from the SCI injured population differed significantly from a normal control population. The results support the concept that DTI has the potential to provide quantitative information that supplements the neurologic examination.

Hypothesis

The objective of this study was to determine if specific advanced MRI features of SCI can be utilized to - better stratify patients at the time of presentation of injury. We proposed to develop a novel schema for classifying SCI utilizing the neurologic exam at presentation (AIS), conventional MRI feature designators

of lesion length and location, as well as, additional MRI metrics provided by DTI to determine which variables or combination of variables best predicts clinical outcome. We intended to validate this method as a novel set of biomarkers that can be used to forecast recovery in the acute period after SCI. A practical application of this method is early selection of patients who would benefit for administration of novel therapies that need to be administered acutely.

Review of Specific Aims

The purpose of this project was to develop a novel objective method to assess the extent of neurologic damage in acute SCI utilizing advances MR imaging techniques. The specific aims for this proposal were:

I. To determine whether advanced MRI features of spinal cord injury can be used as an objective surrogate for the neurologic examination given by the NLI and AIS in assessing the acute SCI patient.
II. To determine if absolute changes in FA, apparent diffusion coefficient (ADC), longitudinal/axial diffusivity (AD) and transverse/radial diffusivity (RD) provided by DTI correlate with the extent of spinal cord injury and degree of neurologic deficit.
III. To determine if absolute changes in FA, ADC, AD and RD provided by DTI in SCI deviate from normal overall as well as in proportion to the degree of neurologic deficit.
IV. To determine which combination of variables obtained from the traditional neurologic exam at the time of presentation of injury, conventional MRI features of SCI (given by length and location of spinal cord hemorrhage and edema), and diffusion characteristics of the spinal cord (given by DTI) yield the most precise means to stratify neurologic deficits and future clinical outcome.
V. To determine if MRI can be used to discriminate patients with incomplete injuries who have the capacity for spontaneous functional recovery from those with poor inherent capacity for recovery.

Methods

Project Proposal Summary: We proposed to recruit eighty cervical SCI patients and twenty control patients without SCI admitted to our Level I trauma and spinal cord injury center (RSCICDV) over a 24 month period. At the time of admission, patients would be assessed with a full INSCSCI motor and sensory examination and assigned an impairment grade and a neurologic level of injury based upon the AIS criteria. Patients would also be evaluated with MRI to assess the degree of spinal cord damage. This would include a DTI acquisition that encompassed the entire length of the cervical spinal cord. The lesion will be characterized for presence of edema/hemorrhage and mapped against the anatomic segments of the cervical spine. In addition, derived diffusion characteristics (i.e., FA, MD, LD and TD) of the entire cervical spinal cord would be mapped in correspondence to the anatomic level. Each patient's progress would be monitored from the initial hospitalization acute care through six months after injury and serial motor and sensory evaluations would be performed at fixed time points.

Patient Population and Clinical Assessment

One hundred men and women, at least 21 years of age, who were evaluated at the Thomas Jefferson University Hospital Level 1 Regional Resource Trauma Center and Regional Spinal Cord Injury Center of the Delaware Valley (RSCICDV) were proposed as the enrollment cohort in this study. The 100 patients would include eighty (80) patients with isolated cervical injuries and twenty (20) trauma patients with no neurologic deficit who were being screened with MRI for ligamentous injury who would serve as normal controls.

The inclusion criteria for the spinal cord injury patients were: (1) complete initial clinical assessment of motor power within 24 hours following injury and a final assessment of motor power no earlier than six months after the injury; (2) referred for a clinically indicated MRI study of the cervical spine obtained

within twelve hours of the initial injury; (3) injuries resulting from non-penetrating trauma; and (4) isolated cervical spinal cord injuries from neurological levels C3-T1. The controls were trauma patients with no neurologic deficit who were being screened with MRI for ligamentous injury. The exclusion criteria are: (1) contraindication for MR imaging, (2) concurrent thoracic spinal cord injury/peripheral nerve injury and (3) clinically significant chronic illnesses or neurologic co-morbidity that would, in the opinion of the investigator, preclude participation in this study.

Those determined eligible to participate in the study were identified by the rehabilitation medicine co-investigator and approached by them or the rehabilitation medicine research study staff to consider participation in the study. The study was explained to the patient and the patient was given time to consider the risks and benefits of the study and ask questions about participation. The consent form was reviewed with the patient and the patient and a study investigator signed the consent form.

Clinical examinations: Neurologic assessments (Task 4ab) were conducted: (1) within 24-hours of injury, (2) one week post-injury, (3) two weeks post-injury (4) 3 months post injury, (5) 6 months post injury. All neurological examinations were performed by examiners trained according to the International Standards for Neurological Classification of Spinal Cord Injuries (INSCSCI). Sensation for light touch and pin prick was tested in the 26 paired dermatomes from C2 through S4-5, using a 3-point scale (0-2). Motor function was assessed by performing manual muscle testing on the 5 key muscles in each extremity, scored on a 6-point scale (0-5). For the upper extremities, these muscles include the biceps, radial wrist extensors, triceps, flexor digitorum profundus, and the abductor digiti minimi. For the lower extremities, these muscles consist of the hip flexors, knee extensors, tibialis anterior, extensor hallucis longus, and the gastro-soleus. Total scores were obtained by adding together the individual scores for light touch (maximum score 112), pin prick (maximum score 112), upper extremity motor (UEMS - maximum score 50) and lower extremity motor (LEMS - maximum score 50). Digital rectal examination was performed to determine the presence or absence of deep anal sensation or voluntary motor contraction of the anal sphincter. At each neurologic assessment subjects were classified for neurological level of injury (NLI), sensory level of injury, motor level of injury, completeness of injury, and ASIA impairment scale grade. At the 6-month post-injury assessment, the self-care subscale of the Spinal Cord Independence Measure (SCIM) was used to evaluate functional recovery of the upper extremities, and the Walking Index for Spinal Cord Injury (WISCI-II) to evaluate lower extremity functional recovery. In cases of missing assessments, the medical records and therapy notes were reviewed to score the SCIM and WISCI-II. This was done for 2 SCIM scores and 9 WISCI levels.

Since the diffusion values reflect more than just corticospinal track integrity, an additional clinical scale was applied to the SCI cohort that is a composite of motor and sensory (pin and light touch) scores below the level of injury. This was a modification of the Yale Scale Score for spinal cord trauma (YSS) (74). The original YSS calculated an average score for light touch and pin prick scores in dermatomes below the level of injury, for motor scores in muscles below the level of injury, and a score for deep pain appreciation. These scores were then added to give a composite score of neurologic function below the injury ranging from 0 to 10 (2 points for LT, 2 points for PP, 5 points for motor, and 1 point for deep pain appreciation). In our study deep pain appreciation was not tested, so the modified YSS had a maximum of 9 points. For consistency, since all subjects had cervical level injuries, the scores for dermatomes from T2 through S4-5 and the scores of LE muscles were averaged at the initial and final clinical assessment time points. Incorporation of the modified YSS into the outcomes data potentially provides a more comprehensive assessment of clinical functionality.

Magnetic Resonance Imaging Anatomic and Diffusion Protocol

MR imaging: MR imaging was conducted on a 1.5 Tesla (Achieva, Philips Healthcare, Netherlands), superconducting unit. Minimum imaging included four scans in the sagittal and axial planes. T1 and T2 weighted spin-echo sagittal sequences will be obtained using the following parameters: 22 cm field of view, 4 mm slice thickness with a 1 mm gap and a 192 x 256 matrix as part of patients clinical care

assessment. Examples of parameters for T1-weighted images include TR/TE(600/9), 2 NEX and for the T2-weighted images, TR/TE(2000/30/80), 1 NEX or fast spin echo acquisition TR/TE (2000-3000/20 effective TE / 80-102 effective TE), a 256x256 matrix, ETL 8, 2-4 NEX. An additional sagittal sequence was performed using gradient echo methods, (e.g. TR/TE(50/15), flip angle 15^{o}). Flow compensation techniques were utilized in the T2-weighted and gradient echo sequences. The field of view incorporated the lower brainstem, the entire cervical spinal cord and upper thoracic region. Cross-sectional images used gradient echo techniques to achieve relative T2* weighting. Using this latter technique, 9 cm of the cervical spinal cord was evaluated, extending from the C2-3 disc space to the upper margin of T1 (Task 3a).

Diffusion Tensor Imaging: As a supplement to the clinically indicated MRI an additional diffusion tensor imaging (DTI) acquisition sequence was performed (Task 3b). This utilized a non-proprietary, vendor provided DTI pulse sequence that was modified and optimized for the cervical spinal cord. An implicit requirement of the devised DTI protocol was that it had to be straightforward enough to instantiate and acquire by any trained MR technologist at any time of the day without immediate physics support. The supplemental diffusion tensor acquisition (DTI) consisted of a single shot non-cardiac gated echo planar (EPI) technique. The 3.7-minute acquisition using six diffusion directions (Bo=800) and eight signal averages, using 128x128 resolution (0.95 mm voxels) in the axial plane resulting in 36-40 contiguous 3 mm thick axial sections of the entire cervical spinal cord. Sequence parameters were TR:6200, TE: 82, NSA: 8, FOV: 220x130 mm, Matrix: 144x144, 36 slices, 4 mm slice thickness with in-plane resolution of 1.53x1.53 mm. A rotating frame of reference system was employed to ensure that the z-axis of the DTI acquisition was angled parallel to the long axis of the spinal cord to account for variations in spine angulation and positioning.

By year 2 an alternate acquisition technique became available from the MR vendor that purported to provide substantial improvement in DTI image quality by reducing artifact caused by susceptibility changes. This method was based upon the ZOOM-EPI (zonally magnified oblique multislice echo planar imaging) technique proposed by Wheeler et al. (75). The ZOOM-EPI technique was tested and determined to provide similar image quality at improved spatial resolution in a similar acquisition period with an observed difference in normalized values from the standard DTI EPI method. A second set of twenty control subject DTI datasets were therefore collected to provide normalized data for the ZOOM-EPI method as subject enrollment proceeded. The acquisition protocol was then changed such that all subsequent enrolled patients would have DTI data collected with the new method. Sequence parameters for the ZOOM EPI were TR:4950, TE: 95, NSA: 4, FOV: 110x110 mm, Matrix: 96x96, 32 slices at 4 mm slice thickness with in-plane resolution of 1.15x1.15 mm/voxel.

Non-rigid registration was performed at the scanner of the DTI data to correct for local motion mis-registration artifacts and both the composite data and the individual slice repetition data was transferred to the clinical PACS and a commercial workstation (Philips EDW Workstation) for quality control assessment and analysis.

Conventional MR imaging assessment: All spinal cord trauma images were evaluated by one of the two neuroradiologists who were blinded to the clinical status of each patient (Tasks 5a-c). The quality of the imaging study overall was recorded. The morphology, length and location of the spinal cord lesion was assessed on mid-sagittal MR images. Longitudinal reference points were generated along the length of the cervical spinal cord which will serve as an independent variable specifying distance from lesion epicenter. Morphology (edema and hemorrhage) was assessed using two characteristics seen on MRI: (1) cord edema as indicated by intramedullary hyperintensity on T2-weighted sagittal images, and (2) acute cord hemorrhage (deoxyhemoglobin) as indicated by focal decreased signal on T2-weighted and sagittal gradient echo images. The length of edema and hemorrhage was measured to determine the amount of damaged tissue that is expected to be directly related to the degree of initial neurologic impairment.

The location of the damage to the spinal cord was quantified by locating the longitudinal boundary of the

spinal cord hemorrhage and edema relative to the nearest adjacent spinal vertebral landmark as described previously (30). Each vertebral body will be divided into three equal parts: the upper half, mid-portion and the lower half, segments 1, 2, and 3 respectively. The intervertebral disc below each vertebral body was defined as segment 4. The anatomic location was expressed by the portion of the closest vertebral body which intersects a horizontal line drawn through the lesion (Task 5ab) (Figure 1). Each segment location from C2 to T1 was rank ordered yielding 28 possible locations. Using this method, four discrete locations representing the upper (rostral) and lower (caudal) limits of edema and hemorrhage were recorded. A fifth location was recorded which corresponded to the approximate center or impact zone of the injury. The rostral-caudal location is directly related to the degree of neurologic impairment in the upper extremities. Assessment of spinal cord swelling was deferred as its inherent value in predicting neurologic deficit is minimal.

DTI image evaluation: The DTI data from each MR exam was transferred to an independent workstation for post-processing by a physicist with extensive experience in diffusion pulse sequence design and DTI post processing and analysis (Task 6a). Utilizing multiple DTI specific post-processing packages, including a custom in-house developed DTI processing analytical pipeline application, image co-registration was performed followed by white matter thresholding to remove the contribution of gray matter to the derived values (Task 6b). An automated, step-wise, voxel-by-voxel registration process was performed for each slice repetition and for each slice location. Datasets were checked for goodness of fit as part of the quality assurance process. Whole cord FA, MD, LD (λ_1) and TD (λ_{23}) were calculated for each of the contiguous slice locations. A graphical representation of the entire span of the cervical spinal cord was then created for ADC and FA values to assess for drift and to subjectively assess for injury patterns.

When the MR physicist and personnel were inadvertently recruited to another university in the middle of the grant cycle (June 2013) it was decided to abandon the in-house analytical QC pipeline for a more manual process using a commercially available workstation (Philips EDW, Netherlands). The DTI analysis was repeated for all subjects on this standard platform (Task 6c). While the analytical pipeline offered rapid quality control of the datasets, it suffered from automation bias in consistently selecting white matter voxels at the expense of gray matter and peripheral white matter with resultant loss of potentially useful information.

The DTI data analysis methodology was modified accordingly to better accommodate intersubject anatomic variability and to provide better one-to-one correspondence when performing comparisons between patients and controls. We adopted the methods of Mulcahey etal (76) in which holocord regions of interest were manually drawn around the perimeter of the spinal cord on axial source data at seven key anatomic locations corresponding to the level of the atlas, followed by the six successive interspaces. This ensured uniformity in comparing DTI parameters between patients and controls and allowed for more direct comparison of values for subsequent analysis. Regions of interest were manually drawn on the corresponding source DTI axial image along the perimeter of the spinal cord for each of the seven anatomic locations. Mean FA, ADC and principle eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) we recorded at each level. Mean diffusivity (MD) and radial diffusivity (RD) were derived from these measures (Task 6c).

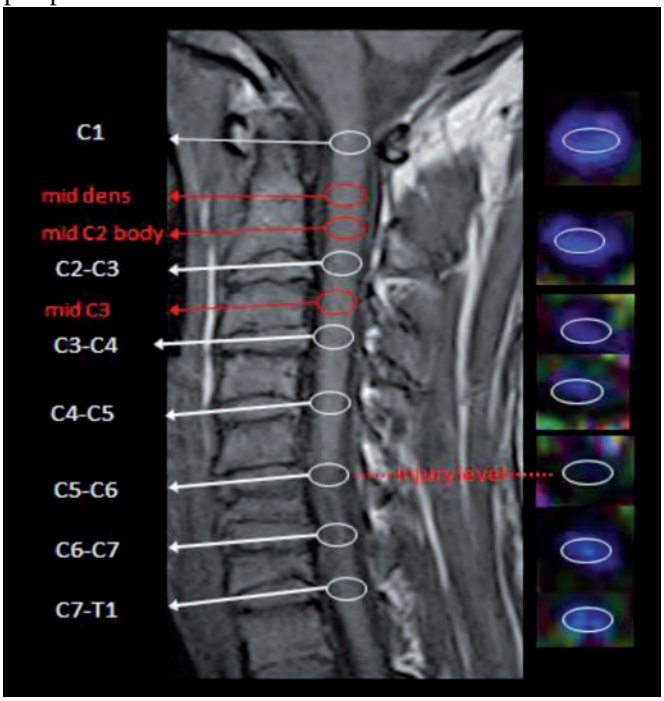

Figure 3. Anatomic location of the seven key DTI regions of interest (ROI) obtained for each SCI patient and control. From Mulcahey et al. Spine 2012;37:E797-E803.

Data Manipulation and Analysis

As there was no a priori relationship between the MRI measures of injury and the clinical measures of injury and recovery, an exploratory analysis was performed using all possible permutations between the independent MRI values and the dependant clinical outcomes parameters.

The anatomic MRI parameters used for the analysis included the length of edema and hemorrhage, location of lesion center which were derived from the upper and lower limits of both features (Tasks 5a-c). The location of maximal compression and the anterior-posterior and transverse dimensions were used to calculate a compression ratio (ie AP/transverse). The anatomic levels were recoded into categorical values and unit-less length measures for hemorrhage and edema were derived from the location values.

For the DTI measures, FA, ADC and principle eigenvalues from each of the seven measured levels were used to generate mean FA, ADC, RD, AD (longitudinal) values. Additional derivations included minimal, maximal and entire cord mean values for each DTI parameter. DTI values were also recorded from the anatomic level corresponding to the anatomic center of injury.

DTI parameters are known to vary by level in the normal human cervical spinal cord. To verify the variances between the adjacent spinal levels a Bartlett test was applied followed by an examination of 1-way repeated measure of variance, considering each spinal level as an intra-subject variable.

Two DTI techniques were used in this study: single-shot EPI and single-shot ZOOM EPI, each of which generates different absolute values for FA, ADC, RD, LD and the principle eigenvalues.

The 20 control subjects collected for each EPI method were employed to transform the patient data into the normalized values using a z-score in the methods described by Uda et al. [patient value – mean control value/standard deviation of control value] (77). Z-scores were calculated for each DTI parameter at each location for every patient relative to the corresponding mean control value at the same location in the normal dataset for each acquisition technique. Minimum, maximum and mean z-scores were also calculated for each patient. Z scores were used primarily as the independent variables for DTI when testing for correlations with the clinical parameters (Task 6d).

Aggregate clinical scores were derived from the serial INSCSCI examinations. The INSCSCI exam consists of multiple parts including: an American Spinal Injury Association (ASIA) impairment scale (AIS) designated by a score ranging from A (motor/sensory complete with sacral sparing) to D (sensory incomplete), a neurologic level of injury (NLI), a manual muscle test (MMT) and a sensory examination consisting of light touch and pinprick assessment for twenty-eight dermatomes on each half of the body.

Composite scores for NLI were generated from the four motor/sensory scores. Aggregate muscle function was assessed using manual muscle test (MMT) evaluations (score 0 to 5) for the five key muscles in each extremity (25 per extremity) for a total possible motor index score (MIS) of 100 (5/muscle x 5muscles/extremity x 4 extremities) (Task 4c). Upper extremity (UE) and lower extremity (LE) MIS subtotals were generated at each of the five examination timepoints (when available). Finally a modified composite motor and sensory score was generated using the Yale Scale Score (YSS) providing a relative weighting of lower extremity motor and sensory scores for a total possible score of 9. Aggregate scores always included values from both the patients left and right sides.

Improvement in motor function was determined by comparing an initial UEMS or LEMS (at time of admission) to a final MS (at 6 months). A MS recovery rate (RR) was calculated using the method of Lucas and Ducker (78) which represents the actual change in MS relative to the largest potential improvement in MS, given the initial score and the maximum possible score.

A second measure of motor function, the number of muscles with minimally useful function, was also derived from the individual muscle scores (Task 4e). The total number of individual muscles capable of minimally useful motor function (antigravity strength or better) at least 6 months post-injury was compared to the number at the time of injury. This value is expressed as a percentage of the total number of muscles measured (ten muscles in the upper extremities, ten in the lower extremities).

Clinical recovery was assessed by the method of Lucas & Ducker (78) (final – initial)/(maximum – initial) to yield a recovery rate between zero and one. Rather than using a simple percent difference, this calculation accounts for potential capacity for recovery based upon maximum potential score. The Lucas & Ducker recovery rate was applied to final and initial recorded motor (MIS) and YSS scores.

A dichotomous score for SCI severity was created by stratifying patients into two groups based upon initial MIS for the lower extremities using a threshold of 30 (50 maximum). Similarly, a dichotomous recovery score was calculated using a combination of recovery rates for lower extremity useful muscles and YSS with a threshold of 0.5. These were additional derived outcomes parameters that were tested against.

Final functional outcome for the upper and lower extremities was also assessed using two additional clinical instruments: the self-care subscale of the Spinal Cord Independence Measure (SCIM) for the upper extremities (maximum score 20) and in subjects with incomplete injuries, we used the mobility subscale of the SCIM (when available) and the Walking Index for Spinal Cord Injury (WISCI-II) to evaluate lower extremity functional recovery (maximum score 20).

Analysis

The cardinal DTI values of fractional anisotropy (FA), apparent diffusion coefficient (ADC), transverse or radial diffusivity (RD) and axial or longitudinal diffusivity (LD) were transformed into z-scores using methods described previously using matched corresponding anatomic levels and DTI techniques (77).

Each patient DTI dataset was co-registered by lesion center. Analysis of variance (ANOVA with Dunnet-Hsu adjustment) was performed for the entire dataset to determine statistically significant differences in the cardinal DTI values indexed for each position measured from the lesion epicenter.

As there were no a priori assumptions about the relationship between the anatomic MRI or DTI data relative to the clinical assessment an exploratory assessment was performed that compared all MRI/DTI parameters (independent variables) against all neurologic subscores as well as recovery (dependent variables). To compare this non-parametric datasets, Spearman rank-order correlation was used to identify heretofore expected and unexpected relationships between dependent and independent variables. Significance was set at < 0.05.

An ROC analysis was performed using the independent variables that exhibited the strongest correlation with neurologic deficit and recovery to determine the accuracy of various DTI z-scores in predicting presence or absence of SCI and in discriminating good from poor recovery. Presence or absence of SCI was stratified by a MIS of less than 30 (50 total possible) for the lower extremities. Recovery was stratified by a threshold of greater than fifty percent recovery rate as calculated by Lucas & Ducker.

RESULTS

Patient Enrollment

Meeting recruitment obligations was a consistent challenge throughout the enrollment period. Opening of recruitment was delayed for six months while awaiting final IRB approval from the Department of

Defense. Overall, recruitment was primarily jeopardized by a marked decrease in spinal cord injury referrals to our institution. Prior to this grant cycle, the average number of spinal cord injured (SCI) patients referred to the Regional Spinal Cord Injury Center of the Delaware Valley (RSCICDV) at Thomas Jefferson University Hospital averaged over one-hundred annually, with the majority categorized as cervical injuries. No definitive regional analysis has been performed but factors that have come into consideration include: (1) retention of SCI patients at outside local facilities for acute care and rehabilitation, (2) relative decrease in incidence of spinal cord injury regionally and (3) referral to other acute care facilities. The fact that annual admissions to our network rehabilitation hospitals (e.g. Magee, Moss and Bryn Mawr) remained high is secondary supportive evidence that acute management of regional SCI patients has been taking place at other acute care or level I trauma facilities.

During the recruitment period, 568 spinal and spinal cord injured patients received care at RSCICDV at TJUH. 105 of the RSCICDV patients were designated as cervical spinal cord injures at the time of admission. The 82 (~80%) of patients who were not recruited for this study were excluded for a number of reasons ranging from unexpected changes in disposition, incomplete MR evaluations and comorbidities that excluded them from eligibility. The most common etiology for non-eligibility in the study were from pre-existing comorbidities from dementia, drug and alcohol dependency (23 patients), language barriers (5 patients), prior cervical cord injury or surgery (7 patients), additional spinal injuries (2 patients), metastatic disease (1 patient) or medical instability (8 patients). These pre-existing problems precluded performing accurate serial neurologic exam or would confound the results of the neurologic examinations. Ten patients who were eligible for this study refused to consent after the research protocol was explained to them. Seven patients who were eligible were transferred out of the system to receive acute care. A total of nineteen potential patients were excluded due to inadequate or incomplete MRI data. This included eight studies in which the diffusion tensor imaging (DTI) data was not acquired during the admission MRI or the DTI was deemed of poor quality (1 study). Eleven patients arrived to RSCICDV at TJUH with an MRI of the cervical spine performed at an outside facility and received immediate surgical intervention before a local DTI assessment could be performed at TJUH. Overall, of all patients who were eligible to participate, 70% were successfully recruited for the study and 72% of all patients who were eligible for the study received a diagnostic quality MRI and DTI examination excluding those who arrived at our facility with an MRI performed elsewhere.

Patient demographics

Twenty-three acute cervical SCI patients were registered in the study since approval for open enrollment (month 6), (Task 2a, months 36-42). Our cohort included 17 males and 6 females. Ages ranged from 25 to 81 (mean age of 53). Cohort demographics included thirteen white males, five white females, three black males, one black female and one Hispanic male. All patients were assessed to meet study inclusion criteria (Task 2b) and informed consent was reviewed and obtained from each patient (Task 2c). The initial patient was enrolled on 8/25/2011 and the last patient on 4/14/2014.

Distribution of impairment by American Spinal Injury Association (ASIA) scale on admission included: A (1); B (5); C (6); D (11). Distribution by neurologic level of injury (NLI) included: C1 (1); C2 (3); C3 (1); C4 (5); C5 (8); C6 (3); C8 (2). There were no patients characterized as C7 injuries by International Standards for Neurological Classification of Spinal Cord Injury (ISNSCI) criteria.

Patient retention/compliance for the entire six-month clinical evaluation period following injury was variable. One patient expired and nine patients officially withdrew from the study before the six-month clinical evaluation. Eight patients did not return or withdrew from the study by the time of the three-month clinical evaluation.

Diffusion Tensor Imaging (DTI)

Composite graphs of the cardinal DTI values for the entire patient cohort co-registered to injury level and

converted to z scores are shown in (Figure 5). Visual inspection of the composites show a clear trend in which the DTI metrics of FA, ADC and transverse diffusivity (RD) all sharply deviate from baseline at the lesion center (position 0) as expected with reduction in FA and concomitant elevation in ADC and RD. There was no significant change in longitudinal (AD) diffusivity across the span of the cervical cord. There are nine levels represented which include the level of the injury center in addition to four levels above and below the center (+4 and -4). Tests for differences in values across the nine levels using least squares (model estimated) comparisons as well as pairwise comparison between lesion epicenter and indexed positions (+/-4) from center for FA, ADC, and transverse diffusivity (RD) there is clear evidence that the average scores differ by level ($p<0.0001$). For longitudinal diffusivity (AD), there is no significant difference ($p=0.36$). For FA and transverse diffusivity (RD), the adjusted pairwise comparisons show that the average z-score at the lesion center is lower than all positions. By contrast there was a broader profile of ADC across the length of the spinal cord such that a significant difference in ADC is demonstrated only beyond +/- 2 indexed locations from lesion epicenter. The strongest visual relationship between perturbations in DTI score and injury is consistently identified for FA and transverse (RD) diffusivity.

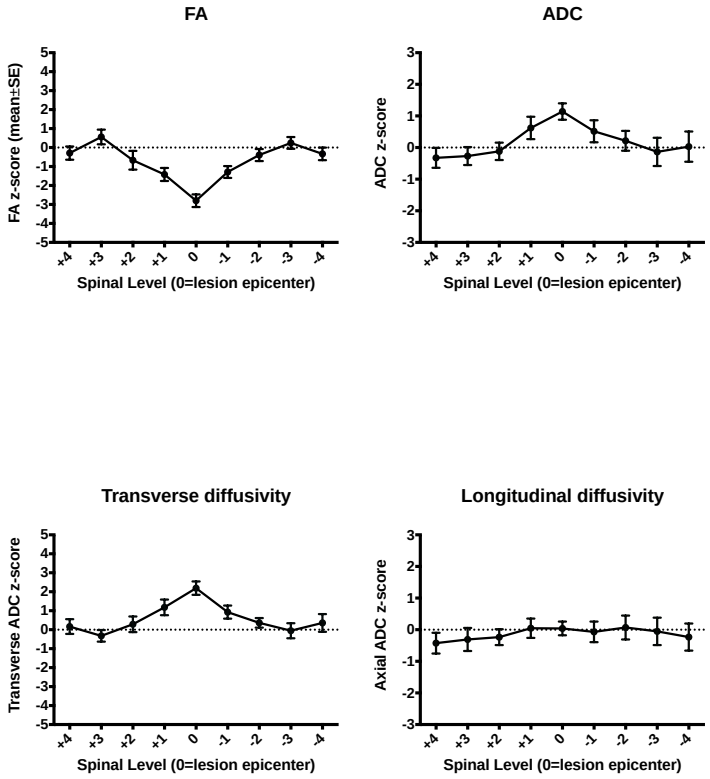

Figure 5. Composite graph of FA, ADC, radial and axial diffusivity z-scores versus relative spinal level co-registered to the injury level. Note that the injury zone is well depicted as a significant deviation from baseline in all parameters except longitudinal.

Correlation of MRI Anatomic Injury to Neurologic Deficit/Recovery

The primary anatomic MR parameters were cord compression and length of spinal cord hemorrhage and edema. These were derived from the location of the upper and lower limits of hemorrhage and edema respectively. Spearman correlations between length of spinal cord edema/hemorrhage and the neurologic parameters at each time point are provided in Table I. Edema and hemorrhage length strongly correlated to many of the early and late clinical attributes for neurologic deficit and recovery. Moderately strong negative correlations ($p<.05$) with total motor index scores (MIS) and lower extremity MIS was realized at all time points. There was expected lack of correlation with upper extremity MIS as lesion location was not accounted for in the analysis and will need to be addressed in an upcoming multivariate analysis. Similarly, moderately strong negative correlations between length of spinal cord edema/hemorrhage were found with the Yale Scale Score (YSS) and total number of useful muscles (ie individual muscle MIS of 3 or larger) and the AIS (ASIA impairment scale) at all time points. In aggregate total MIS, total useful muscles and YSS at the six-month evaluation correlated with the extent of injury on the initial MRI. No useful relationship was found between neurologic status at any time point and the cord compression ratio.

Relationships between the length of spinal cord edema/hemorrhage were also found with recovery parameters (Table 2) although not to same extent as with the neurologic scores at each time point. Lower extremity motor recovery, recovery of useful muscle function in the lower extremities and in aggregate were related to length of edema and hemorrhage on the initial MRI. The two measures of functional outcome obtained at six months, (SCIM and WISCI) were also predicted by these MR measures of spinal cord injury. Length of edema had a very strong correlation with SCIM ($r=-0.733$, $p=0.002$).

Correlation of the Cardinal DTI Features to Neurologic Deficit and Recovery

As shown in Figure 5, there was a consistent trend for reduction in FA, elevation in ADC and transverse diffusivity (RD) in proximity to the focus of injury. There was no significant change in longitudinal diffusivity with lesion proximity. The correlations between the z-scores calculated for the cardinal DTI features of FA (fractional anisotropy), ADC (apparent diffusion coefficient), RD (radial/transverse diffusivity) and AD (axial/longitudinal diffusivity) measured at the SCI lesion center are given in Table 3. Several significant relationships between DTI metrics and neurologic impairment were revealed only for FA, while the other features did not demonstrate any strong relationship with the neurologic parameters. The FA measured at the anatomic level of injury exhibited a moderate correlation with lower extremity motor scores obtained at one week after injury (r=0.458, p=0.037), the one-week ASIA impairment grade (r=0.526, p=0.014), useful lower extremity muscles at one-week (r=0.439, p=0.046) and at two-weeks (r=0.490, p=0.039), and total useful muscles at two-weeks (r=0.525, p=0.025). The minimum FA value (not shown) also correlated with one week ASIA score and the number of useful muscles in the lower extremities and in total at two-weeks. Minimum FA is likely very similar to the FA measured at the lesion center.

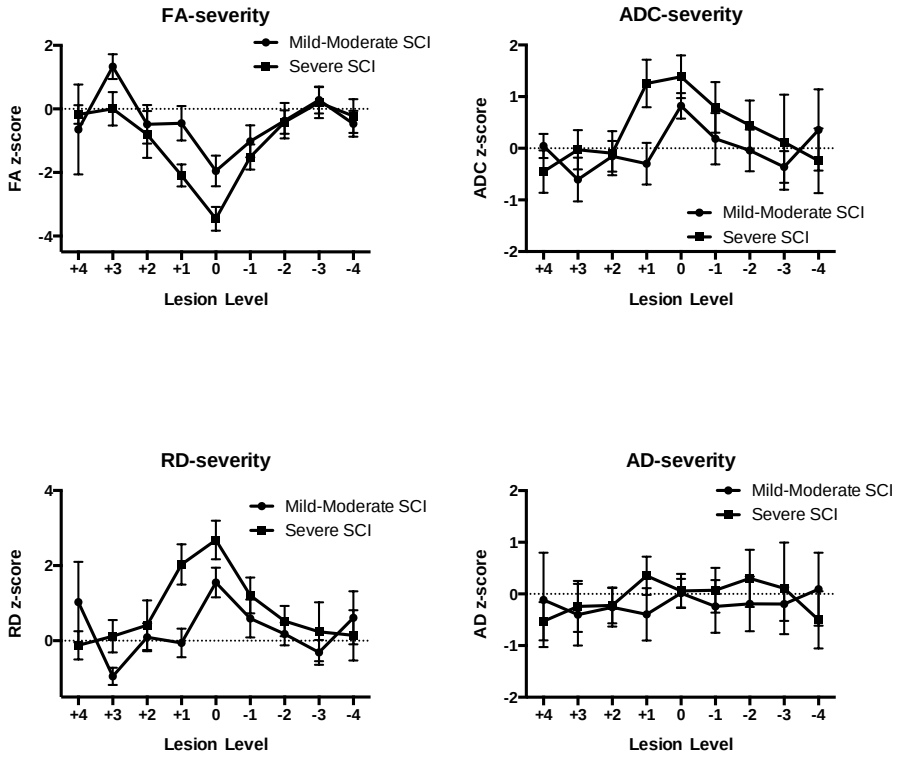

Figure 6. Cardinal DTI values by proximity to lesion center for patients dichotomized by severity of initial motor index score in the lower extremities (severe: MIS LE < 30). Patients co-registered by injury epicenter as in Figure 5.

Figure 6 also shows the relationship of the DTI z-scores relative to the proximity of injury center for patients dichotomized based upon severity of initial lower extremity motor index scores (MIS), with the severe category designated as an MIS LE < 30 (50 maximum total). The nadir for FA, ADC and RD persists however there is a clear demarcation in the magnitude of change for each parameter based upon injury severity at the level of injury for all but AD. Mild injuries (i.e. MIS LE ≥ 30) in general had lower FA, ADC and RD z-scores relative to the severe category (i.e. MIS LE < 30). There was no apparent discriminatory value of axial diffusivity (AD).

While FA measured at the lesion center at the time of injury showed the strongest correlations to a number of neurologic deficit parameters, it was not significantly correlated to neurologic recovery (Table

4) with the exception of exhibiting a moderately positive correlation with the six-month WISCI evaluation (r=0.500, p=0.029). However, ADC at the injury level moderately correlated with lower extremity motor recovery (r=-0.459 p=0.028), modified YSS recovery (r=-0.479, p=0.021) and recovery of useful lower extremity muscles (r=-0.443, p=0.034). Of note is that while ADC z-scores did not correlate with either the six-month SCIM or WISCI functional evaluation there was a correlation to the dichotomous recoding (good/poor) categories. Transverse or radial diffusivity z-scores showed a moderate negative correlation to several recovery parameters including motor recovery in the legs (r=-0.457, p=0.028), change in Yale Scale Score (r=-0.534, p=0.009). Maximum ADC showed a similar relationship to the recovery parameters inasmuch it was a close surrogate for ADC measured at injury, as ADC was frequently at maximum in close proximity to the lesion center.

Patients were also dichotomized into two lower extremity (LE) recovery groups based upon change in motor score using the recovery rate calculation of Lucas & Ducker; good recovery for a recovery of > 0.5 and poor recovery for a calculation ≤ 0.5, Figure 7. Compared to initial MIS scores there is clear discrimination between the two recovery groups based upon all four cardinal DTI features obtained at the level of injury and in the immediate proximity to the level of injury. "Good" recovery was denoted by lower FA, ADC, RD and AD z-scores compared to "poor" recovery. The effect is more discriminatory for ADC, radial (RD) and axial diffusivity (AD) where there is no discernable overlap. Also of note is that the profiles of the curves differ by DTI type; FA and radial diffusivity changes are most dependent upon proximity to the lesion center whereas ADC and axial diffusivity changes span a larger distance of the spinal cord.

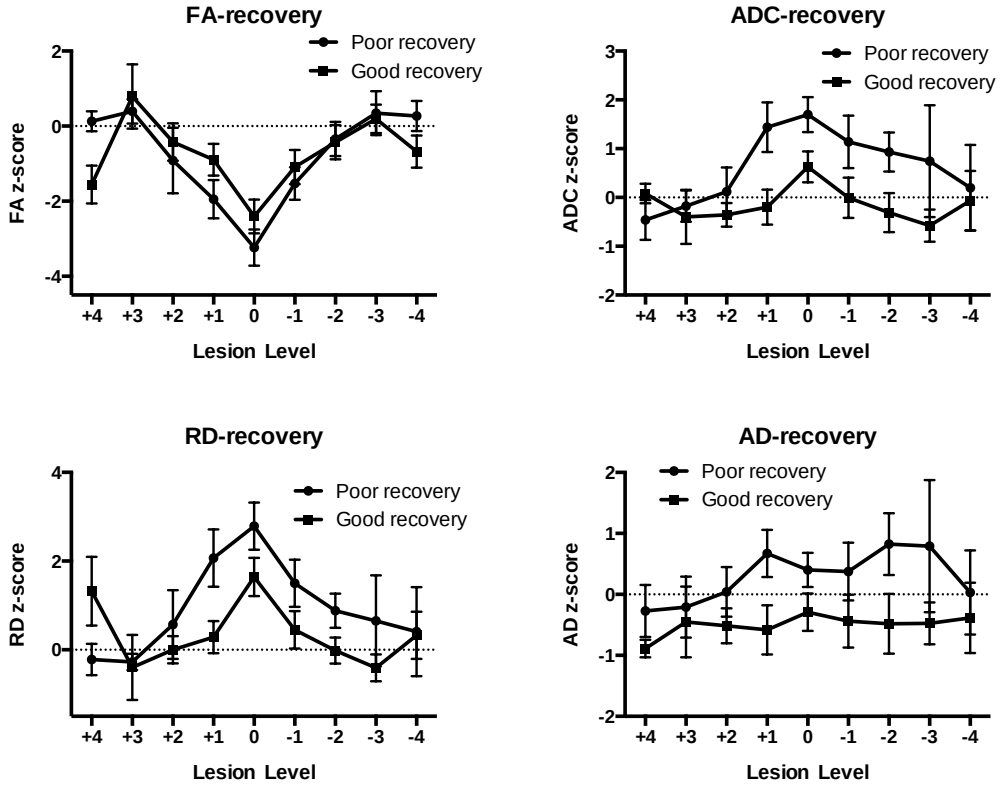

Figure 7. Cardinal DTI z-scores by proximity to lesion center for patients dichotomized into good and poor recovery subgroups using a recovery rate threshold of 0.5.

As the center of injury is often the most compressed level from associated anatomic distortion the reliability of the values obtained at this level may differ from those obtained at adjacent levels. An exploratory analysis of correlations with the dependent clinical variables was performed for each adjacent index levels from lesion center. Spearman correlations for the four cardinal DTI z-scores at the anatomic

level immediately *cranial* to the lesion epicenter are shown in Table 5. Compared to the identical comparison performed at the SCI lesion center there was an obvious increase in the number of statistically significant correlations with the neurologic parameters and the magnitudes of the correlations on average were more substantial. Whereas FA was the most significant DTI feature at the injury level, FA, ADC, radial and axial diffusivity *immediately adjacent to the lesion center* all showed a relationship to the neurologic assessment at various time points. This relationship was not observed for any of the other adjacent levels cranial or caudal to lesion center.

In addition, different relationships were also observed for the recovery parameters when compared to the DTI z-scores obtained one level cranial to the injury center (Table 6). In this analysis, ADC and RD showed the largest proportion of significant correlations with the recovery indices compared to either FA or AD. FA measured above lesion center related best to total MIS recovery rate ($r=0.441$, $p=0.040$), final SCIM ($r=0.521$, $p=0.041$) and WISCI (strongest correlation, $r=0.624$, $p=0.006$). ADC measured above the lesion center correlated best with lower extremity recovery. Radial diffusivity (RD) exhibited moderate correlation with most of the recovery parameters. AD had the weakest and least significant correlations overall to the neurologic recovery indices.

Accuracy and Discriminatory Power of the DTI Indices

Receiver operator characteristic (ROC) analysis was performed to test the accuracy and discriminatory power of the highly correlative DTI parameters found in the preceding exploratory analysis. Significance was confirmed at $p<0.05$ using the Mann-Whitney U test to ensure 95% confidence intervals. Figure 8 shows the ROC analysis in discriminating spinal cord injury from normal. The area under the curve (AUC) was significant for maximum transverse diffusivity (RD) (AUC 0.854), ADC maximum (AUC 0.713) and FA minimum (AUC 0.892). Figure 9 shows the results of the ROC analysis using the four DTI z-scores measured in thee adjacent locations: lesion epicenter and one station above and below the lesion center. The test was to discriminate mild from severe SCI using an arbitrary threshold of 30 for lower extremity motor index score (MIS). The AUC was significant ($p<0.05$) for FA measured at injury center and above (AUC 0.769 and 0.833 respectively), ADC and RD measured above lesion center (AUC 0.750 and 0.824 respectively). No significant discriminating power was demonstrated for axial/longitudinal (AD) diffusivity. Finally, an ROC analysis was performed for the four cardinal DTI z-scores measured at and +/- one level above and below injury center to determine if lower extremity recovery can be discriminated with DTI based upon a dichotomized threshold for lower extremity recovery rate of 0.5. AUC was significant ($p<0.05$) for ADC measured at center, above and below injury (AUC 0.791, 0.782 and 0.755 respectively), longitudinal/axial diffusivity (AD) at center and above (AUC 0.746 and 0.746 respectively) and radial diffusivity (AUC 0.736). No significant discriminating power was demonstrated for FA in this instance.

Limited assessment of upper extremity function and recovery has been performed thus far for this reason the central focus of our analysis has been on lower extremity function. Upper extremity analysis requires accounting for neurologic level of injury as an additional independent variable. This may also aid in subsequent modeling of the zone of partial preservation of injury (ZPP) for upper extremity recovery. Multivariate analysis is currently ongoing. Moreover, specific combinations of DTI, anatomic MRI and initial clinical indices may provide better insight into forecasting recovery than any single parameter.

Table 1. Spearman correlations between anatomic MRI features and clinical parameters at specified intervals. (MIS = motor index score, LE = lower extremities, UE=upper extremities).

		Cord Edema		Cord Hemorrhage	
Neurologic Feature	Time Point	(p value)	(r value)	(p value)	(r value)
MIS LE	Initial	**0.042***	-0.619	**0.000***	-0.591
	7 day	**0.016***	-0.532	**0.004***	-0.605
	14 day	**0.000***	-0.770	**0.021***	-0.526
	90 day	**0.005***	-0.702	**0.000***	-0.530
	180 day	0.093	-0.531	**0.000***	-0.549
MIS Total	Initial	0.111	-0.508	0.603	-0.168
	7 day	**0.016***	-0.532	**0.031***	-0.471
	14 day	**0.000***	-0.782	0.062	-0.436
	90 day	**0.009***	-0.666	0.089	-0.454
	180 day	**0.025***	-0.668	**0.000***	-0.597
Yale Scale Score	Initial	**0.016***	-0.674	**0.000***	-0.669
	7 day	**0.002***	-0.642	**0.006***	-0.582
	14 day	**0.001***	-0.730	**0.023***	-0.519
	90 day	**0.002***	-0.761	**0.000***	-0.523
	180 day	**0.009***	-0.741	**0.000***	-0.642
# Useful Muscles UE	7 day	0.084	-0.396	0.376	-0.204
	14 day	**0.002***	-0.678	0.241	-0.283
	90 day	0.058	-0.518	0.209	-0.344
	180 day	**0.000***	-0.604	**0.000***	-0.476
# Useful Muscles LE	Initial	0.060	-0.582	**0.000***	-0.537
	7 day	**0.006***	-0.594	**0.007***	-0.573
	14 day	**0.000***	-0.761	0.069	-0.439
	90 day	0.077	-0.487	**0.000***	-0.483
	180 day	0.104	-0.516	**0.000***	-0.514
# Useful Muscles Total	Initial	0.346	-0.315	0.482	-0.225
	7 day	**0.014***	-0.542	0.044	-0.443
	14 day	**0.000***	-0.789	0.166	-0.341
	90 day	**0.015***	-0.632	**0.000***	-0.516
	180 day	**0.042***	-0.619	**0.000***	-0.697
ASIA Impairment Score	Initial	0.097	-0.526	**0.000***	-0.620
	7 day	**0.007***	-0.580	**0.009***	-0.558
	14 day	**0.001***	-0.739	**0.000***	-0.603
	90 day	**0.017***	-0.669	**0.000***	-0.394

Table 2. Spearman correlations between anatomic MR parameters and measures of neurologic recovery. (UE = upper extremity, LE = lower extremity)

Recovery Parameter	Cord Edema		Cord Hemorrhage	
	(p value)	(r value)	(p value)	(r value)
Upper Ext MIS	0.132	-0.331	0.753	0.070
Lower Ext MIS	**0.032***	-0.459	0.174	-0.293
Total MIS	0.086	-0.374	0.383	-0.191
Yale Scale Score	0.058	-0.411	0.231	-0.260
SCIM	**0.002***	-0.733	**0.000***	-0.435
WISCI	**0.035***	-0.498	**0.015***	-0.549
UE useful muscles	0.064	-0.401	0.769	-0.065
LE useful muscles	**0.007***	-0.557	0.150	-0.310
Total useful muscles	**0.007***	-0.555	0.196	-0.280

Table 3. Spearman correlations between cardinal DTI z-scores measured at the SCI lesion center compared to neurologic parameters obtained at specified intervals.

Neurologic Feature	Time	FA at lesion		ADC at lesion		RD at lesion		AD at lesion	
		p value	r value	p value	r value	p value	r value	p value	r value
MIS LE	Initial	0.178	0.416	0.429	-0.240	0.653	-0.145	0.528	-0.347
	7 day	**0.037***	0.458	0.366	-0.208	0.276	-0.249	0.928	-0.128
	14 day	0.211	0.301	0.571	-0.139	0.465	-0.178	0.925	0.088
	90 day	0.322	0.273	0.559	-0.150	0.813	-0.067	0.466	-0.175
	180 day	0.138	0.459	0.186	-0.138	0.509	-0.211	0.198	0.305
MIS TOT	Initial	0.407	0.263	0.224	-0.375	0.396	-0.270	0.253	-0.190
	7 day	0.063	0.412	0.231	-0.273	0.196	-0.294	0.676	-0.021
	14 day	0.145	0.348	0.249	-0.278	0.209	-0.302	0.884	0.023
	90 day	0.507	0.186	0.474	-0.200	0.657	-0.125	0.368	-0.190
	180 day	0.229	0.374	0.416	0.257	0.996	-0.002	0.384	-0.129
Modified YSS	Initial	0.211	0.371	0.659	0.135	0.775	0.088	0.562	-0.354
	7 day	0.078	0.393	0.484	-0.162	0.317	-0.229	0.987	-0.097
	14 day	0.132	0.358	0.383	-0.212	0.272	-0.265	0.920	-0.036
	90 day	0.639	0.132	0.714	-0.104	0.940	0.021	0.490	-0.250
	180 day	0.238	0.368	0.753	0.102	0.816	-0.075	0.737	0.275
# Useful Muscles UE	Initial	0.722	0.114	0.123	-0.450	0.296	-0.329	0.120	-0.454
	7 day	0.159	0.319	0.272	-0.251	0.257	-0.259	0.618	-0.115
	14 day	0.350	0.227	0.241	-0.283	0.356	-0.224	0.447	-0.186
	90 day	0.844	0.056	0.422	-0.185	0.808	-0.069	0.268	-0.267
	180 day	0.223	0.386	0.617	0.110	0.977	-0.009	0.594	0.174
# Useful Muscles LE	Initial	0.254	0.355	0.479	-0.157	0.812	-0.077	0.631	-0.086
	7 day	**0.046***	0.439	0.402	-0.193	0.309	-0.233	0.939	-0.018
	14 day	**0.039***	0.490	0.406	-0.209	0.147	-0.356	0.915	0.027
	90 day	0.275	0.301	0.077	-0.330	0.408	-0.231	0.059	-0.359
	180 day	0.124	0.474	0.191	-0.124	0.499	-0.217	0.209	-0.110
# Useful Muscles Total	Initial	0.491	0.219	0.279	-0.328	0.483	-0.224	0.300	-0.314
	7 day	0.073	0.399	0.387	-0.199	0.276	-0.249	0.868	-0.039
	14 day	**0.025***	0.525	0.374	-0.223	0.118	-0.381	0.936	0.020
	90 day	0.418	0.224	0.283	-0.275	0.582	-0.155	0.193	-0.335
	180 day	0.104	0.495	0.758	0.100	0.842	-0.065	0.720	0.116
ASIA Impairment Score	Initial	0.055	0.578	0.176	-0.355	0.324	-0.312	0.404	-0.200
	7 day	**0.014***	0.526	0.397	-0.195	0.200	-0.291	0.968	-0.009
	14 day	0.063	0.462	0.394	-0.099	0.388	-0.224	0.679	0.108
	90 day	0.352	0.279	0.108	-0.367	0.418	-0.246	0.061	-0.437
	180 day	0.194	0.424	0.176	-0.168	0.696	-0.133	0.129	-0.244
SCI Severity (boolean) (Initial LE MIS LE<30)	Initial	**0.021***	-0.479	0.290	0.230	0.115	0.337	0.925	0.021

Table 4. Spearman correlations between cardinal DTI z-scores measured at the SCI lesion center compared to various neurologic recovery parameters.

Recovery Parameter	FA at lesion		ADC at lesion		RD at lesion		AD at lesion	
	p value	r value	p value	r value	p value	r value	p value	r value
MIS Upper Extremities	0.729	0.076	0.202	-0.276	0.177	-0.292	0.128	-0.250
MIS Lower Extremities	0.119	0.334	**0.028***	-0.459	**0.028***	-0.457	0.466	-0.327
MIS All Extremities	0.177	0.292	0.197	-0.279	0.081	-0.372	0.389	-0.160
Modified Yale Scale Score	0.061	0.396	**0.021***	-0.479	**0.009***	-0.534	0.745	-0.189
# Useful Muscles Upper	0.912	0.024	0.120	-0.333	0.225	-0.263	0.087	-0.365
# Useful Muscles Lower	0.164	0.300	**0.034***	-0.443	0.056	-0.405	0.139	-0.318
# Useful Muscles Total	0.532	0.137	0.147	-0.312	0.202	-0.276	0.169	-0.297
MIS LE/# LE useful muscle recovery (boolean, good v. poor) (recovery < vs >0.5)	0.221	0.265	**0.036***	-0.440	0.106	-0.346	0.113	-0.340
YSS recovery (boolean, good v. poor) (recovery < vs >0.5)	0.305	0.224	**0.005***	-0.561	**0.037***	-0.437	**0.040***	-0.430
SCIM score	0.142	0.384	0.754	-0.040	0.615	-0.136	0.745	0.088
WISCI score	**0.029***	0.500	0.249	-0.278	0.120	-0.369	0.830	-0.053

Table 5. Spearman correlations between cardinal DTI z-scores measured at the *adjacent cephalad level* from SCI center compared to various neurologic parameters.

Clinical Features	Time	FA above lesion		ADC above lesion		RD above lesions		AD above lesion	
		p value	r value	p value	r value	p value	r value	p value	r value
MIS LE	Initial	**0.042***	0.603	0.054	-0.564	**0.028***	-0.631	0.622	-0.154
	7 day	**0.029***	0.489	0.164	-0.324	**0.039***	-0.465	0.970	0.009
	14 day	**0.015***	0.563	**0.023***	-0.531	**0.004***	-0.637	0.899	0.033
	90 day	**0.049***	0.540	**0.007***	-0.680	**0.007***	-0.687	0.493	-0.194
	180 day	0.092	0.514	0.070	-0.275	0.109	-0.486	0.248	0.360
MIS TOT	Initial	0.327	0.308	0.190	-0.403	0.216	-0.385	0.105	-0.483
	7 day	0.094	0.385	0.352	-0.220	0.151	-0.333	0.407	-0.196
	14 day	**0.026***	0.522	0.105	-0.394	**0.017***	-0.553	0.144	-0.359
	90 day	0.116	0.442	**0.038***	-0.565	**0.022***	-0.604	**0.029***	-0.575
	180 day	**0.037***	0.617	0.853	-0.039	0.143	-0.449	0.147	-0.174
Modified YSS	Initial	0.155	0.418	0.496	-0.204	0.180	-0.396	0.327	-0.305
	7 day	**0.035***	0.474	0.155	-0.330	**0.043***	-0.457	0.618	-0.119
	14 day	**0.021***	0.540	0.084	-0.418	**0.013***	-0.575	0.362	-0.228
	90 day	0.181	0.380	**0.033***	-0.578	**0.035***	-0.565	0.128	-0.429
	180 day	0.243	0.364	0.703	-0.119	0.301	-0.326	0.591	0.171
# Useful Muscles UE	Initial	0.782	0.089	0.262	-0.329	0.406	-0.264	0.310	-0.296
	7 day	0.318	0.235	0.873	-0.038	0.573	-0.134	0.949	0.015
	14 day	0.120	0.380	0.232	-0.297	0.071	-0.435	0.500	-0.170
	90 day	0.206	0.359	0.111	-0.400	0.069	-0.499	0.266	-0.272
	180 day	0.211	0.395	0.502	0.055	0.339	-0.303	0.480	0.229
# Useful Muscles LE	Initial	0.148	0.445	0.097	-0.438	0.089	-0.512	0.155	-0.370
	7 day	**0.029***	0.488	0.111	-0.368	**0.026***	-0.496	0.343	-0.224
	14 day	**0.003***	0.693	**0.018***	-0.517	**0.002***	-0.687	0.192	-0.269
	90 day	0.179	0.383	**0.015***	-0.518	0.082	-0.480	**0.030***	-0.458
	180 day	0.097	0.506	0.091	-0.235	0.132	-0.460	0.191	-0.129
# Useful Muscles Total	Initial	0.429	0.250	0.249	-0.349	0.251	-0.360	0.353	-0.282
	7 day	0.087	0.393	0.415	-0.193	0.157	-0.329	0.757	-0.074
	14 day	**0.006***	0.652	0.073	-0.410	**0.007***	-0.629	0.417	-0.169
	90 day	0.078	0.489	**0.026***	-0.575	**0.017***	-0.626	0.096	-0.439
	180 day	0.051	0.582	0.321	-0.137	0.112	-0.483	0.690	0.046
ASIA Impairment Score	Initial	**0.017***	0.689	**0.022***	-0.600	**0.010***	-0.711	0.310	-0.478
	7 day	**0.005***	0.597	0.053	-0.438	**0.009***	-0.566	0.073	-0.245
	14 day	**0.018***	0.591	**0.019***	-0.483	**0.008***	-0.640	0.297	-0.319
	90 day	0.178	0.398	**0.002***	-0.692	**0.021***	-0.629	0.103	-0.641
	180 day	0.113	0.516	**0.040***	-0.377	**0.000***	-0.551	**0.006***	-0.261
SCI Severity (boolean Initial MIS LE < or >30)	Initial	**0.015***	-0.512	**0.027***	0.471	**0.009***	0.544	0.239	0.262

Table 6. Spearman correlations between cardinal DTI z-scores measured at the *adjacent cranial level* from SCI center compared to various neurologic recovery parameters.

Recovery Parameter	FA above lesion		ADC above lesion		RD above lesion		AD above lesion	
	p value	r value	p value	r value	p value	r value	p value	r value
MIS UE	0.223	0.271	0.254	-0.254	0.293	-0.235	0.088	-0.168
MIS LE	0.058	0.410	**0.031***	-0.460	**0.039***	-0.443	0.502	-0.372
MIS Total	**0.040***	0.441	0.172	-0.302	0.108	-0.352	0.161	-0.151
Modified YSS	0.060	0.407	0.052	-0.419	**0.040***	-0.441	0.406	-0.309
# Useful Muscles UE	0.234	0.265	0.094	-0.366	**0.040***	-0.298	0.162	-0.309
# Useful Muscles LE	0.071	0.392	**0.026***	-0.475	0.177	-0.436	0.066	-0.398
# Useful Muscles Total	0.095	0.365	0.067	-0.398	**0.042***	-0.380	0.174	-0.301
MIS L# LE useful muscle recovery (boolean, good v. poor) (RR < vs >0.5)	0.129	0.333	**0.016***	-0.506	**0.026***	-0.473	**0.037***	-0.448
Modified YSS (boolean, good v. poor RR < vs>0.5)	0.431	0.177	**0.034***	-0.454	0.076	-0.385	**0.037***	-0.446
SCIM score	**0.041***	0.521	0.150	-0.332	**0.031***	-0.539	0.406	-0.177
WISCI score	**0.006***	0.624	0.180	-0.331	**0.037***	-0.495	0.538	-0.155

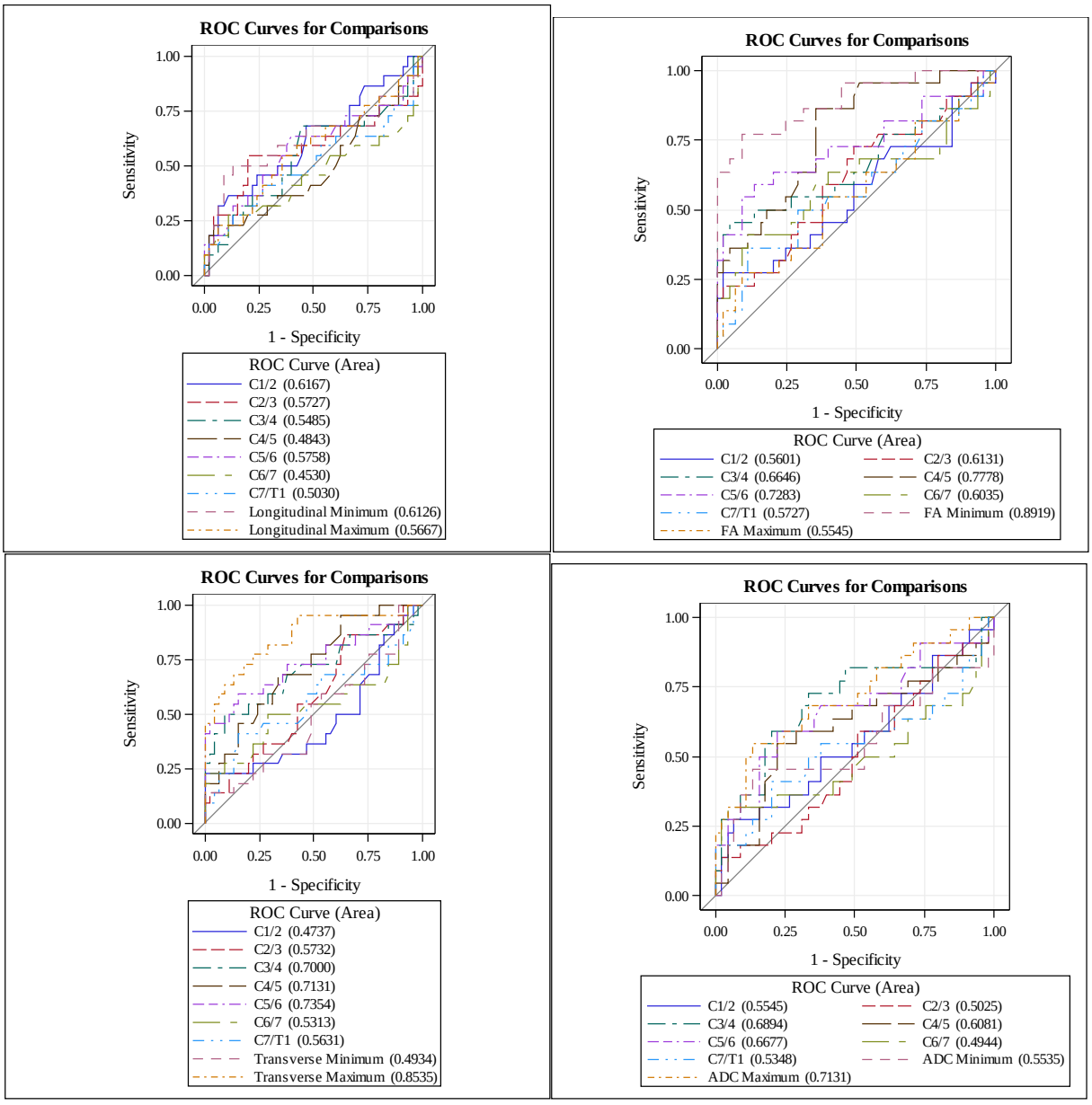

Figure 8. ROC analysis for the four cardinal DTI z-scores measured at all anatomic locations and minimum/maximum values in discrimination of spinal cord injury from normal. AUC is significant ($p<0.05$) for transverse maximum (RD) (AUC 0.854), ADC maximum (AUC 0.713) and FA minimum (AUC 0.892)

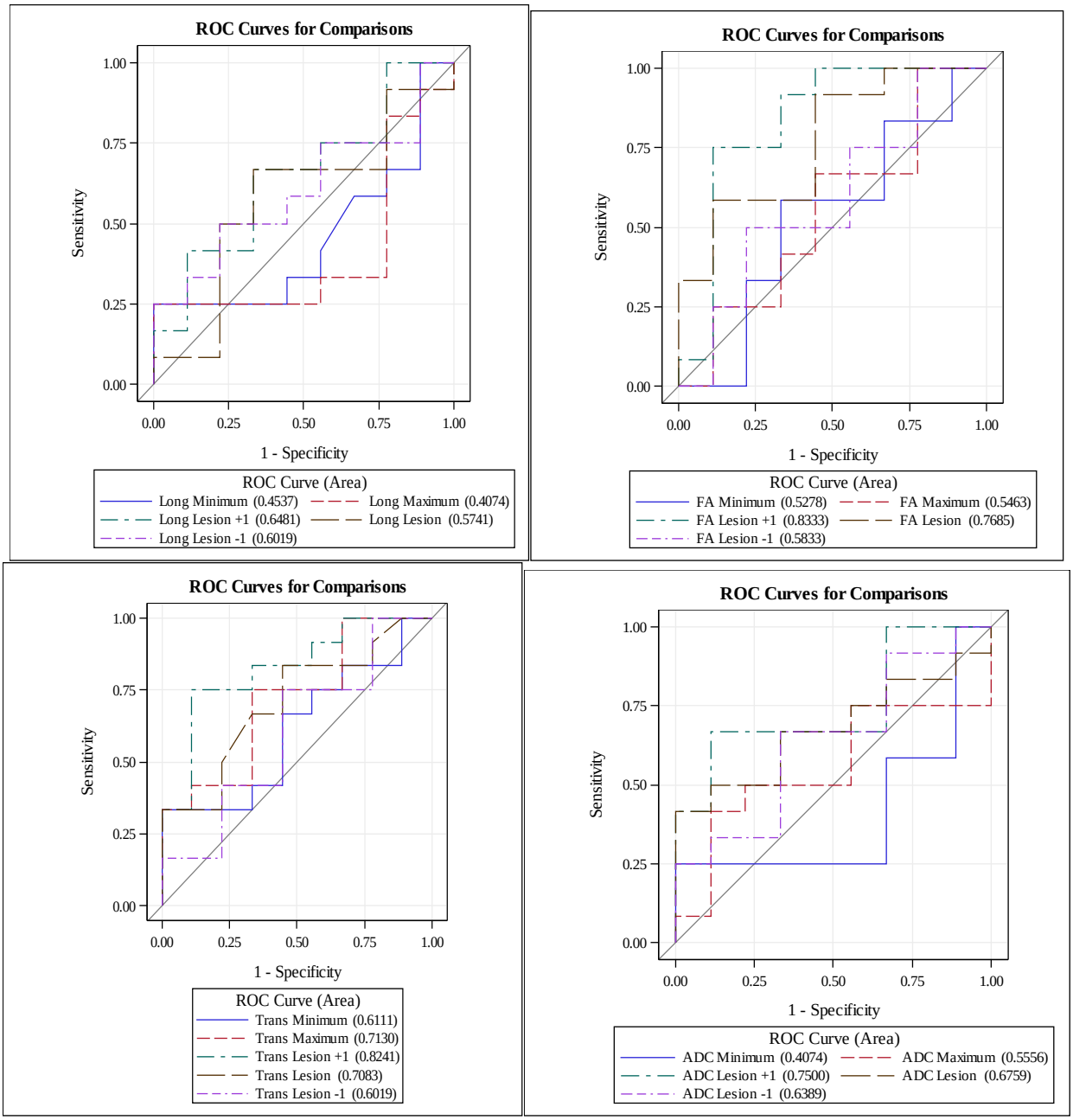

Figure 9. ROC analysis for the four cardinal DTI z-scores measured at and +/- one level above and below injury in discrimination of severity of spinal cord injury based upon a dichotomized threshold of 30 for lower extremity MIS. AUC was significant ($p<0.05$) for FA measured at injury center and above (AUC 0.769 and 0.833 respectively), ADC and RD measured above lesion center (AUC 0.750 and 0.824 respectively). No significant discriminating power was demonstrated for axial/longitudinal diffusivity.

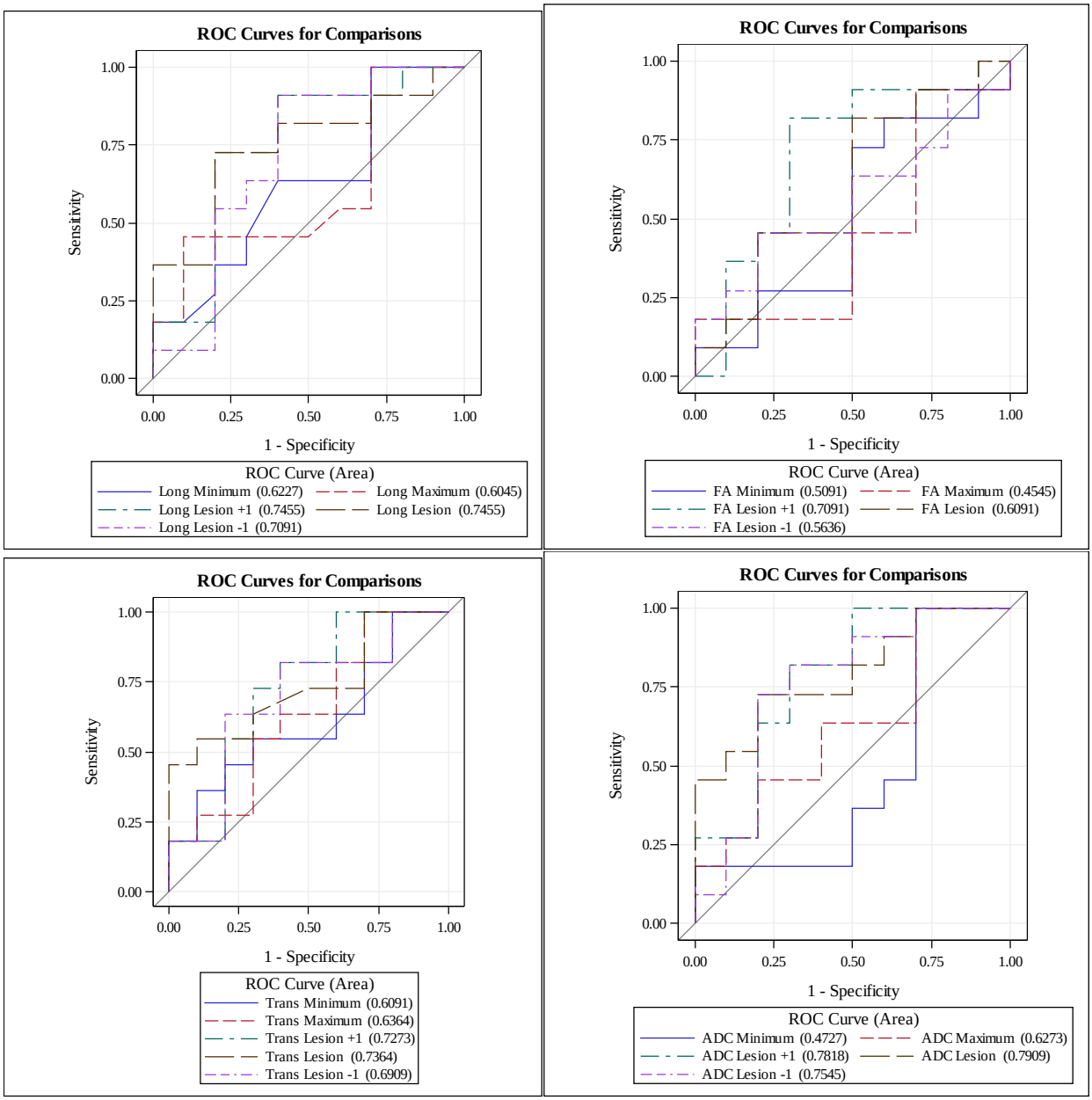

Figure 10. ROC analysis for the four cardinal DTI z-scores measured at and +/- one level above and below injury in discrimination of lower extremity recovery based upon a dichotomized threshold for lower extremity recovery rate of 0.5. AUC was significant ($p<0.05$) for ADC measured at center, above and below injury (AUC 0.791, 0.782 and 0.755 respectively), Longitudinal or axial diffusivity (AD) at center and above (AUC 0.746 and 0.746 respectively) and radial diffusivity (AUC 0.736). No significant discriminating power was demonstrated for FA.

Key Research Accomplishments

- We developed and implemented a commercially viable spinal cord DTI MRI protocol using an FDA approved vendor sequence that is practical both from a time investment and in its ability to be setup and acquired by any trained MR technologist without support from a MR physicist.
- We have shown that a single-shot ZOOM-EPI DTI protocol is technically superior to a conventional single-shot EPI DTI protocol in assessing the human spinal cord.
- We have shown that it is both feasible and practical to measure and analyze the spinal cord injury DTI data using commercially available vendor provided workstation/software instead of with proprietary algorithms.
- This rapidly acquired DTI data shows consistent changes in all of the cardinal MR features (FA, ADC, RD and AD) that are proportional to the proximity to the anatomic center of the injury.
- Length of spinal cord edema and hemorrhage on anatomic MRI exhibit strong correlations with neurologic injury and recovery after spinal cord injury.
- FA, ADC and RD DTI values obtained at the time of injury may be useful in discriminating severity of spinal cord injury.
- FA, ADC and RD DTI values obtained at the time of injury may be useful in identifying patients who have potential for good recovery after injury.
- DTI indices measured immediately cranial to the actual lesion epicenter exhibit consistently stronger correlations and accuracy in predicting neurologic injury and recovery than indices measured at the lesion center.
- Different DTI indices may harbor varied implications regarding initial neurologic injury and subsequent recovery.

Conclusion

Although this investigation was confounded by limitations in patient recruitment and retention, the results overall are compelling regarding the implications of using MRI and DTI as a surrogate for the neurologic examination. In contrast to prior studies, our imaging protocol is both practical and efficient and is accessible to most facilities with modern 1.5T MR systems. We utilized vendor provided and FDA approved software for our acquisitions and analysis. Even in the absence of advanced proprietary imaging, post-processing and analytical methods, our results were consistent with numerous prior DTI studies for experimental and human SCI. We consistently observed proportional elevations in ADC and RD with corresponding reduction in FA that reached a maximum in proximity to the SCI epicenter. While standard MR features of hemorrhage/edema length correlate very well with the neurologic parameters and recovery characteristics, the DTI indices also show complementary relationships to many of the INSCSCI clinical scales and reveal that the DTI profile may help to discriminate SCI patients. Unique to this study was the exhaustive comparison to the majority of the neurologic instruments in common use for evaluation of SCI.

There is a compelling argument for supporting the routine use of MRI and DTI as part of the standard initial clinical assessment of the SCI patient. The results of this study and from existing published works suggest that anatomic imaging of the injured spinal cord in combination with the physiologic data derived from DTI offers a surrogate classification system for neurologic examination that can provide an objective assessment of the damaged spinal cord. The extent of spinal cord dysfunction from SCI is inferred through the INSCSCI evaluation. The neurologic evaluation is very granular and comprehensive. Under ideal conditions, with a skilled and experienced examiner and a highly cooperative patient, the metrics derived are very accurate, reproducible and carry prognostic implications for the patient and family. Under less than ideal conditions, the value of the neurologic exam is less clear and the classification of a patient using unreliable clinical data confounds our capability to understand potential for neurologic recovery. Moreover, as the emphasis in the acute care setting has changed towards urgent decompression of the spinal cord with concomitant stabilization, it has become impractical to obtain a detailed neurologic assessment at the time of initial admission. These impediments are sharply divergent from the requirement to rapidly classify an SCI patient for potential recruitment into a clinical trial for a novel therapy. Injection of the agent into the exposed thecal sac or spinal cord at the time of initial decompressive surgery would likely offer the patient the most expedient clinical benefit.

While MRI and DTI will likely never provide the same high level of granularity as that of a good quality neurologic examination, it does offer three distinct advantages over the INSCSCI assessment: (1) speed, (2) objectivity and direct visualization of the end organ (the spinal cord). Pharmacologic companies that are engaged in development of SCI therapeutics not only need a reliable measure of neurologic function (ie the clinical examination) but they also rely upon MR imaging to demonstrate the intrinsic changes to the spinal cord immediately after injury and temporally after direct administration of a therapy. As such, it may be more suitable to select a patient for a clinical trial primarily on the basis of the MRI and DTI findings and secondarily on the initial neurologic assessment.

The results derived from this study do actually provoke a number of fundamental questions, some of which may be answered with continued multivariate analysis of the existing data. The marked increase in significant correlations for DTI measures obtained *cephlad* to injury center remains perplexing. This may simply be a reflection of the inherent difficulty in obtaining accurate measures at the most damaged portion of the spinal cord. It is also not evident why some of the DTI indices have value for neurologic injury and others are more highly correlated to recovery. Differences in DTI profiles along the length of the spinal cord require are not completely evident and may require more exploration into the physiologic basis of DTI changes in SCI. Recovery in the upper extremities differs from the lower extremities and requires more extensive modeling that accounts for the lesion center and an understanding of the zone of partial preservation of injury (ZPP). The continued analysis of existing data will also likely include more multivariate exploration that will identify the ideal combination of clinical, MRI and DTI characteristics that forecast deficit and recovery.

Publications, Abstracts, and Presentations

1. (abstract) Zohrabian V, Zussman B, Frangos A, Mathews J, Lackey J, Dresner M, Lai S, Marino R, Gorniak R, Flanders AE. Application of Diffusion Tensor Imaging as a Surrogate for Neurologic Deficit in Spinal Cord Injury. Published in the proceedings of the American Society of Neuroradiology (ASNR) Annual Meeting, June 4-9th, Seattle, Washington, 2011.

2. (abstract) Zohrabian V, Zussman B, Frangos A, Mathews J, Lackey J, Lai S, Dresner M, Marino R, Gorniak R, Flanders AE. The "Normal Appearing" Spinal Cord in Spinal Cord Injury: Diffusion Tensor Imaging Alterations Beyond the Visible Zone of Injury. Published in the proceedings of the American Society of Neuroradiology (ASNR) Annual Meeting, June 4-9th, Seattle, Washington, 2011.

3. (abstract) Lai S, Lackey J, Zohrabian V, Zussman B, Dresner A, Shi J, Frangos A, Natale P, Flanders AE. Observer-Related Variability in Spinal Cord Diffusion Tensor Imaging Metrics: Implications in Clinical Research. Published in the proceedings of the American Society of Neuroradiology (ASNR) Annual Meeting, June 4-9th, Seattle, Washington, 2011.

4. (abstract) Zohrabian V, Zussman B, Mathews J, Frangos A, Gorniak R, Lackey J, Dresner MA, Marino R, Lai S, Flanders AE. Can Diffusion Tensor Imaging (DTI) Replace the Neurologic Examination in Spinal Cord Injury (SCI)? Published in the proceedings of the 97th Scientific Assembly and Annual Meeting of the Radiological Society of North America, Chicago, Illinois, November 27th - December 2nd, 2011.

5. (invited lecture) Neuroradiology Series: Spine. Controversies in Cervical Spine Trauma. Presented at the 97th Scientific Assembly and Annual Meeting of the Radiological Society of North America, November 27th - December 2nd, 2011, Chicago, Illinois.

6. (book chapter) Burns AS, Marino RJ, Kramer J, Flett H, Flanders AE, Curt A. Predicting outcome following traumatic spinal cord injury. In: Spinal Cord Medicine, 2nd edition, pp 129-135. Kirshblum S, Campagnolo DI, Gorman PH, Heary RF, Nash MS, eds. Lippincott Williams and Wilkens, Philadelphia, 2012.

7. (invited lecture) Concepts and Controversies in MRI of Spinal Trauma and Spinal Cord Injury. Presented at the American Society of Spine Radiology Annual Symposium, February 16th-19th 2012, Miami, Florida.

8. (invited lecture) Controversies in Spinal Imaging of the Elderly. 3rd Annual Navigating Spinal Care Symposium: Geriatric Spinal Disorders. May 4th, 2012, Philadelphia, PA.

9. (abstract) Zohrabian V, Zussman B, Frangos A, Mathews J, Lackey J, Lai S, Dresner M, Marino R, Gorniak R, Flanders AE. The "Normal Appearing" Spinal Cord in Spinal Cord Injury: Diffusion Tensor Imaging Alterations Beyond the Visible Zone of Injury. Published in the proceedings of the American Society of Spine Radiology Annual Symposium, February 16th-19th, 2012.

10. (abstract) Zoltani Z, Kamali A, Zohrabian V, Dresner M, Gorniak R, Flanders AE. Reliability of Diffusion Tensor Imaging Values in Spinal Cord Injury: Analytical Variations and Effects from Injury Severity. (O-137). Published in the proceedings of the Scientific Assembly and Annual Meeting of the American Society of Neuroradiology, San Diego, California, May 18th – 23rd, 2013.

11. (educational exhibit) Zoltani Z, Zohrabian V, Kamali A, Gorniak RJ, Dresner MA, Flanders AE. Value of MR Imaging and Diffusion Tensor Imaging as Biomarkers for Classifying Acute Spinal Cord Injury (eEdE-175). Published in the proceedings of the Scientific Assembly and Annual Meeting of the American Society of Neuroradiology, San Diego, California, May 18th – 23rd, 2013.

12. (educational exhibit) Zoltani Z, Zohrabian VM, Dresner MA, Gorniak RJ, Chiang DS, Flanders AE. Application of Diffusion Techniques to Common Clinical Problems in Spine Imaging (LL-NRE-WE8A). Published in the proceedings of the 99th Scientific Assembly and Annual Meeting of the Radiological Society of North America, Chicago, Illinois, December 1-6th, 2013.

13. (invited lecture) Controversies in Imaging of the Thoracolumbar Spine. 4th Annual Navigating Spinal Care Symposium: Management of Thoracolumbar Diseases. Philadelphia, PA, May 17th, 2013.

14. (invited lecture) How Useful is MRI in Spine Trauma? American Society of Spine Radiology Annual Symposium, Miami Beach, Florida, February 13th-16th, 2014.

15. (invited lecture) Cervical Spondylotic Myelopathy in The Secrets of Spine Differential Diagnosis (IC110). The American Roentgen Ray Society, San Diego, California, May 4th-9th, 2014.

16. (abstract) Poplawski MM, Gorniak RJT, Dresner MA, Flanders AE. Improved Reliability of Diffusion Tensor Imaging Utilizing Reduced Field-of-View ZOOM-EPI in Normal Human Cervical Spinal Cord. Accepted for presentation to the 100^{h} Scientific Assembly and Annual Meeting of the Radiological Society of North America, Chicago, Illinois, November 30th–December 5th, 2014.

Inventions, Patents and Licenses

Nothing to report.

Reportable Outcomes

Nothing to report.

Other Achievements

Nothing to report.

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Appendices

Nothing to report.